(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification[7]: G01N 33/48

(21) International Application Number: PCT/US02/16962

(22) International Filing Date: 24 May 2002 (24.05.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/311,332   10 August 2001 (10.08.2001)   US

(71) Applicant (for all designated States except US): SYMYX TECHNOLOGIES, INC. [US/US]; 3100 Central Expressway, Santa Clara, CA 95051 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): CARLSON, Eric, D. [US/US]; 10226 Alpine Dr. # 3, Cupertino, CA 95014 (US). CONG, Peijun [CN/US]; 6099 Wellfleet Way, San Jose, CA 95129 (US). CHANDLER, William, H., Jr. [US/US]; 707 Carlsbad St., Milpitas, CA 95035 (US). CHAU, Henry, K. [US/US]; Apartment 34, 475 Cumulus Avenue, Sunnyvale, CA 94087 (US). DANIELSON, Earl [US/US]; 3840 Corina Way, Palo Alto, CA 94303 (US). DESROSIERS, Peter, J. [US/US]; 1745 Nantucket Circle #369, Santa Clara, CA 95054 (US). DOOLAN, Robert, D. [US/US]; 366 West Olive Avenue, Sunnyvale, CA 94086 (US). WU, Luping [CN/US]; Apartment 3, 1283 Ayala Drive, Sunnyvale, CA 94086 (US).

(74) Agents: HENDLER, Pablo, D. et al.; Fish & Neave, 1251 Avenue of the Americas, New York, NY 10020 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: APPARATUSES AND METHODS FOR CREATING AND TESTING PRE-FORMULATIONS AND SYSTEMS FOR SAME

(57) Abstract: The invention provides methods, apparatus, and systems for performing high-throughput preparation and screening of salts and polymorphs of drug candidates. The invention is directed towards enhancing the pre-formulation discovery process used for drug development. In particular, processes that determine suitable salts and processes that discover substantially every polymorph that can form from a particular drug candidate are provided. The processes are performed using several apparatuses that are specifically configured to carry-out various steps in a high-throughput characterization process. One such apparatus is configured for synthesizing a plurality of library members based on, for example, a library model generated by a computer system.

APPARATUSES AND METHODS FOR CREATING AND
TESTING PRE-FORMULATIONS AND SYSTEMS FOR SAME

Cross-Reference to a Related Patent Application

5   This application claims the benefit of United
States Provisional Application No. 60/311,332, filed
August 10, 2001, the disclosure of which is hereby
incorporated by reference in its entirety.

Technical Field of the Invention

10   The present invention relates to the field of
research for pre-formulations or polymorphs. More
particularly, the present invention is directed toward
apparatus and methods for performing parallel synthesis
and screening of salts and polymorphic forms of drug
15 candidates.

Background of the Invention

Combinatorial chemistry has revolutionized
the process of drug discovery. See, for example, 29
Ace. Chem. Res. 1-170 (1996); 97 *Chem. Rev.* 349-509
20 (1997); S. Borman, *Chem. Eng. News* 43-62 (Feb. 24,
1997); A. M. Thayer, *Chem. Eng. News* 57-64 (Feb. 12,
1996); N. Terret, 1 *Drug Discovery Today* 402 (1996)).
Although combinatorial chemistry has to a great extent
eliminated the bottleneck in drug discovery, other

- 2 -

bottlenecks have emerged in getting a drug to market.
One such bottleneck is the selection of salts of active
pharmaceutical ingredients in such drugs. Another is
the identification of polymorphs and pseudo-polymorphs
5   of drug candidates.

A salt of a compound often has
characteristics that are desirable for a drug
candidate, including increased water solubility and a
higher melting point than the compound itself.
10   Further, different salts of a drug candidate may have
disparate and discrete physical properties from one
another. For instance, different salts of a compound
may have different melting points or solubilities, or
may crystallize in different forms and/or under
15   different conditions. Traditional salt selection for a
drug candidate requires mixing (e.g., sometimes
referred to as synthesizing or formulating) a number of
different salts of a compound, recrystallizing the
salts under a number of different conditions to
20   generate a crystalline form, and then characterizing
the salt. This process is time consuming because it
has to be reiterated a number of times to identify
salts with desirable characteristics.

Not only do different salts of a drug
25   candidate have different properties, different
polymorphs of the salt or of the neutral compound may
also have different physical characteristics. As is
known in the pharmaceutical industry, the polymorphic
state of an active pharmaceutical ingredient can change
30   the biological profile of the drug. An industry
journal published an entire special issue on this

- 3 -

topic, *Organic Process Research & Development* (Vol. 4, No. 5, 2000 and in particular pp. 370-435), with the issue pointing out, *inter alia*, that polymorphism and crystallization issues affect many industries as well
5 as pharmaceutical compounds, including explosives, color chemicals and food additives.

Traditional polymorph characterization requires recrystallizing a neutral drug candidate or a drug candidate salt, characterizing the crystals, and
10 comparing the crystals to known forms to identify polymorphs. These steps must be reiterated a large number of times in order to identify all of the polymorphs of a given neutral compound or drug candidate salt. Thus, although characterization of
15 polymorphs is advantageous and, in some cases, necessary, the traditional methods of identifying and isolating polymorphs can be tedious. Crystallizing new polymorphs often requires hundreds to thousands of experiments that analyze the effects of varying
20 critical parameters such as temperature, solvent and solvent mixtures, mixing time, cooling rates, stirring rates, and concentrations and methods and process for precipitation, cooling, evaporation, slurry, and thermo-cycling.

25 One reference in the special issue of *Organic Process Research & Development* discloses the use of a certain technique for the screening of potential salts of pharmaceutically active compounds. Bastin et al. "Salt Selection and Optimisation
30 Procedures for Pharmaceutical New Chemical Entities", *Organic Process Research & Development* 2000, 4,

- 4 -

427-435, incorporated herein by reference. The paper
disclosed a library design for an array of different
salts in different solvents. While this reference
discloses a start at speeding up the pre-formulation
5   process, it fails to follow through with screening in
parallel or with high throughput research into
crystallographic polymorphs.

In addition, several published patent
applications in the area of high throughput or
10   combinatorial materials science disclose a process in
which the materials created in the process can be
screened on the same plate in which they are
synthesized. For example, WO 99/59716 discloses and
claims creating solids on a removable reactor base
15   plate and then performing X-RAY analysis of the solids.
WO 01/34290 and WO 01/34291 reportedly relate to a
"work station" that employs an array that can be
transferred between preparing, screening and
characterization stations without requiring sample
20   handling, preparation or transfer steps. WO 96/11878
also discloses parallel crystallization and screening
of materials on a substrate.

WO 01/51919 also reportedly relates to a high
throughput method for formation, identification and
25   analysis of diverse solid-forms; however, the methods
in this application are extremely broad and vague, such
that the publication serves merely to identify many
problems without providing a solution beyond suggesting
high throughput methods. Other publications reportedly
30   disclose methods of analyzing polymorphs. For
instance, WO 01/82659 reports a method of using X-ray

- 5 -

diffraction to screen polymorphs. The publication
reports that one can compare the X-ray diffraction
pattern acquired for a polymorph and compare it with
the X-ray diffraction patterns of known polymorphs of a
5   compound. However, the publication does not disclose
methods for rapidly generating the polymorph samples or
for using the polymorph comparisons in drug discovery.

Given the rapid process of drug discovery in
the pharmaceutical industry through combinatorial
10 chemistry, a need generally exists in industry for a
combinatorial or high throughput method and apparatus
for the research, discovery and development of
polymorphs formed by drug candidates. However, despite
the cited work, a process for the systematic high
15 throughput research of pre-formulations has not been
directly disclosed.

Summary of the Invention

The present invention addresses this problem
by providing a universal system that addresses the need
20 to characterize drug candidates. The system provides,
inter alia, generation of libraries, salt selection,
polymorph characterization, and other high throughput
methods for identifying and characterizing physical
properties of drug candidates, using a variety of
25 reacting and screening options.

Specifically, the invention provides methods,
systems and apparatus for performing combinatorial or
high throughput preparing, screening and
characterization of drug candidate salts and/or
30 crystalline structures (e.g., polymorphs) of drug

- 6 -

candidates. These methods, systems and apparatus
decrease the time needed to find a suitable form of
active ingredient for formulation and allow for
additional forms of active pharmaceutical ingredients
5   to be discovered, which may allow for additional patent
coverage, a decreased risk of unwanted polymorphs
appearing in later stages of pharmaceutical development
or of competitors discovering a related form. In
addition, the novel apparatus and methods disclosed
10 herein allow for multiple different drug candidates to
be formulated, crystallized and characterized in
parallel, thereby creating a high throughput
methodology for pharmaceutical research organizations
and others.
15   In one aspect, the invention provides a
workflow that enhances the process of identifying and
characterizing potential active pharmaceutical
ingredients (API) from a drug candidate. In one
embodiment of the invention, salts of a drug candidate
20 of interest are formulated using high throughput and/or
combinatorial methods. The drug candidate salts are
then screened to determine a variety of parameters or
properties, which may include, without limitation,
solubility, partition coefficient (log P),
25 crystallinity, hygroscopicity, Raman spectral pattern,
X-ray diffraction (XRD) pattern and melting point. The
data obtained from the screening are then analyzed to
identify suitable drug candidate salts. In a preferred
embodiment, the formulation, screening and analysis are
30 automated. Further, the workflow may be performed
using the apparatus described herein. In another

- 7 -

embodiment, the analysis is performed as the data are
generated so that suitable salts may be rapidly
identified. The workflow may be terminated after a
suitable salt is selected. In a preferred embodiment,
5 the suitable salt is then subjected to polymorph
formulation, characterization and analysis.

        In another aspect, the invention uses high
throughput and combinatorial methods to crystallize,
characterize and analyze polymorphs and/or pseudo-
10 polymorphs of a drug candidate of interest. Generating
and analyzing polymorphs may follow directly after salt
selection or may be performed using an existing drug
candidate. The drug candidate may be a neutral, acidic
or basic compound, or may be a drug candidate salt. In
15 one embodiment, the drug candidate is recrystallized
under a variety of conditions using high throughput
and/or combinatorial methods. The drug candidate
crystals are then screened to determine a number of
characteristics of the crystal, including, without
20 limitation, solubility, log P, crystallinity, melting
point, hygroscopicity, crystal morphology and
birefringence, as well as X-ray diffraction, infrared
(IR), Near IR and Raman spectroscopy, among others.
The data obtained from the screening are then analyzed
25 to identify the crystalline structures of the
recrystallized drug candidate. Polymorphs of a
recrystallized drug candidate may then be categorized
according to the crystalline structure of the
polymorph. In a preferred embodiment, polymorph
30 recrystallization, screening and analysis are
automated, and may be performed with the apparatus

- 8 -

described herein. In another preferred embodiment, the analysis is performed as the data are generated so that different polymorphs and the conditions that produced them may be rapidly identified.

5   The invention further provides a method for selecting solvents for salt selection or polymorph generation. The invention further provides apparatus for high throughput salt preparation, recrystallization, solubility analysis, Raman and X-ray

10   diffraction spectral analysis, and melting point determinations. The invention also provides hardware and software for controlling the salt selection and polymorph characterization methods of the invention and provides systems for automated high throughput

15   operation of these methods.

Thus, one aspect of the invention is directed toward a high throughput method for preparing and characterizing different salts of a drug candidate. In one embodiment, a library is provided having a

20   plurality of library members, wherein each library member comprises at least one drug candidate, and reacting in parallel each of the library members with an acid, base or salt to form different salts (e.g., complex salts or neutrals) of at least one drug

25   candidate. In one embodiment, each library member may further comprise a solvent. In a preferred embodiment, the first library is comprised of at least eight members in regions on a first substrate, wherein the at least eight members comprises at least one drug

30   candidate in an amount of between 0.05 and 50 mg of sample, reacting in parallel each of the at least eight

- 9 -

members with an acid, base or salt to form different,
salts of at least one drug candidate. In another
preferred embodiment, the drug candidate is present in
an amount of less than 10 mg. In a further embodiment,
5   the salts are produced as crystals in glass microtiter
plates by cooling, evaporation, precipitation, slurry,
or solvent gradients of aliquots of hot solutions.

In one embodiment, the drug candidate salts
form crystalline structures. The drug candidate salt
10 crystals and the supernatant or mother liquor may be
left together or may be separated from each other after
the salt reaction step, such that the crystals reside
on the substrate, typically in regions so that the
crystals can be screened individually. The method
15 further provides for screening the crystals to identify
new forms while said crystals reside on the substrate,
as well as screening the supernatant or mother liquor
for solubility of one or more drug candidate salts in
each of the different solvents or solvent mixtures.

20   In general, salts are screened for at least
two properties using various tests such as, for
example, birefringence, melting point, solubility,
hygroscopicity, Raman spectroscopy pattern, crystal
morphology, X-ray powder diffraction pattern, infrared,
25 near infrared or any other suitable test. In another
embodiment, the salts are screened for at least three
properties, four properties or five properties. In one
embodiment, the salts are screened for at least
birefringence, melting point, solubility, Raman
30 spectroscopy pattern and X-ray powder diffraction
pattern.

- 10 -

Another aspect of the invention is polymorph identification and/or characterization of a selected drug candidate. The drug candidate may be a neutral, acidic or basic compound or may be a salt of a drug

5   candidate. In one embodiment, a library is provided and may include a plurality of members that each contain at least one drug candidate and at least one solvent. The library members are subjected to crystallizing conditions in parallel for each of the

10 plurality of members on a substrate in different solvents or solvent mixtures. Each of the members are then screened to identify and/or characterize different crystalline structures of at least one drug candidate. In one embodiment, the library comprises at least eight

15 members in an amount from 0.05 to 50 mg each, preferably less than 20 mg each. In a further embodiment, the polymorphs are produced in glass microtiter plates or other optically transmissive substrate by cooling, evaporation, precipitation by an

20 anti-solvent, slurry, or solvent gradients of aliquots of hot solutions. In another embodiment, the polymorph characterization may be performed with a drug candidate or drug candidate salt without previously having performed salt selection.

25   In a further embodiment, the crystalline structures comprising the crystals and the supernatant or mother liquor is separated from each other after the recrystallization step such that the crystals reside on a substrate, typically in regions so that the crystals

30 can be screened individually or in parallel. The method further provides for screening the crystals for

at least crystallinity while the crystals reside on the substrate, as well as screening the supernatant or mother liquor for solubility of the one or more drug candidates in the different solvents or solvent

5   mixtures. Other screening tests can be selected from a variety of tests, but a sufficient number of tests are performed to make a determination of the number of polymorphs and/or to identify polymorphs or salts thereof that may be suitable for drug formulation.

10   The crystals may be screened for any physical property that would help identify a polymorph. In general, at least two properties are screened. The properties may be birefringence, melting point, solubility, hygroscopicity, IR spectroscopy, Near IR

15   spectroscopy, Raman spectroscopy, crystal morphology, X-Ray powder diffraction pattern or any other suitable screening method. In another embodiment, the crystals are screened for at least three properties, four properties or five properties to identify and

20   characterize polymorphs. In one embodiment, the crystals are screened for at least birefringence, melting point, solubility, Raman pattern and X-ray powder diffraction pattern.

          In one embodiment, crystals may be screened

25   to identify and characterize polymorphs by optically imaging glass microtiter plates or another optically transmissive substrate that contains crystals of drug candidates or salts thereof. Two different optical scanning techniques can be used: transmission and

30   reflection. Optical transmission occurs when an optical signal passes through an array of material

- 12 -

samples. Optical reflection occurs when the optical
signal is reflected by the material sample. Either one
of these scanning techniques determine whether there
are crystalline solids as well as determine the
5 characteristics (size or habit) of any crystals. In
one embodiment, the crystals may be optically imaged
between polarization filters to measure birefringence,
(e.g., to assess crystallinity).

In another embodiment, the crystals are
10 analyzed by birefringence measurements before and after
removal of a supernatant or mother liquor to detect
unstable solvates or hydrates of drug candidates or
salts thereof. In a further embodiment, individual
wells or regions of the optically transmissive
15 substrate may be imaged under magnification (with and
without crossed polarization plates) to determine
crystal habit and size. In yet another embodiment,
scattered light measurements can be used to determine
if there is a crystalline structure. In another
20 embodiment, the crystalline structures may be
characterized by their spectral properties, including,
without limitation, Raman, IR, Near IR or X-ray
diffraction spectroscopy to characterize the crystals
formed on glass microtiter plates or other substrate.
25 Preferred embodiments include Raman and/or X-ray
diffraction spectroscopy. The invention also provides
methods of using software to analyze the spectral data
to identify polymorphs and/or solvates or hydrates
contained in the arrays. In one embodiment, the
30 optical imaging measurements (e.g., birefringence or
crystal morphology), and the spectral measurements

- 13 -

(e.g., Raman and X-ray diffraction) are made on the
same samples without transfer of material from the
substrate.

In another embodiment, the crystalline
5   structures are formed on a glass substrate and/or in an
apparatus that has an optical pathway to the regions or
vessels so that optical measurements can be made while
the crystalline structure is formed (sometimes referred
to herein "in situ" measurements). The crystalline
10   structures may be characterized by their optical or
spectral properties, including, without limitation,
birefringence, Raman spectral pattern, IR pattern, Near
IR pattern, and/or light scattering. In some
embodiments, the apparatus described herein can be used
15   for these in situ measurements.

In another aspect, the melting temperature of
the crystals may be determined. The method involves
the steps of heating glass microtiter plates or other
substrate comprising drug candidates crystallized under
20   different crystallization conditions while making
birefringence, scattering, other optical measurements
to determine melting points, and/or other phase
transitions including but not limited to loss of
molecules of solvent or water from solvated crystals.
25   In a preferred embodiment, the melting point of the
crystals is determined using a parallel melting point
apparatus.

In another aspect, the invention is directed
toward making multiple copies of the arrays by
30   "daughtering" from a parent set of solutions. Thus, in
one embodiment, the invention is directed toward a

- 14 -

method for testing drug candidates using daughter
libraries, comprising forming a library comprised of a
plurality members in regions on a first substrate,
wherein each of the members comprises at least one drug
5   candidate and a different solvent or solvent mixture,
daughtering the members to a plurality of second
substrates to form a plurality of daughter libraries;
and subjecting the daughter libraries to different
crystallization conditions, such as different
10   crystallization methods (e.g., solvent evaporation and
precipitation) and/or different crystallization
parameters (e.g., different temperatures or different
rates of cooling). In another embodiment, daughter
libraries are constructed so that sets of identical
15   crystals can be used in destructive measurements (e.g.,
melting point, hygroscopicity). In another embodiment,
daughter libraries are constructed to archive
libraries.

The various assemblies and computer software
20   of this invention may be combined into a flexible
workflow to identify and characterize polymorphs.
Similarly, the invention also provides a flexible
workflow to identify and characterize different drug
candidate salts.

25   In another aspect, this invention is directed
toward a solvent array, wherein the solvent array is
chosen to achieve a degree of diversity based on an
analysis of solvent parameters. Physical and chemical
properties or other characteristics of the solvents are
30   used to group the solvents into sets based upon
similarities of their physical properties or

- 15 -

characteristics. The number of physical or chemical
properties or characteristics and the number of groups
into which the solvents and solvent mixtures are
clustered determines the type and degree of diversity
5   in the solvent array for a given experiment or assay.
The diverse solvent arrays may be used in the salt
selection and polymorph generation methods described
herein. The invention is also directed toward software
to implement the use of solvent arrays in the methods
10 and systems of the invention.

In another aspect, the invention is directed
toward an apparatus that may be used for preparing an
array of salts or crystals for screening. The
apparatus comprises at least two different assemblies,
15 but preferably three different assemblies, preferably
with interchangeable parts between the different
assemblies. In one embodiment, the apparatus comprises
at least two assemblies, one for solubilizing drug
candidates for recrystallization and/or synthesizing
20 salts of drug candidates (the reactor assembly) and one
for crystallizing the compounds (the crystallization
assembly). In another embodiment, the apparatus
comprises three assemblies, including a reactor
assembly, a filtering assembly and a crystallizing
25 assembly. Futher, one or more of the assemblies are
provided separately (e.g., the filtering assembly).

In one aspect, the reactor assembly may
include a reactor base having an array of a plurality
of receptacles. Each of the receptacles may be
30 isolated from each other to prevent cross-communication
of materials contained therein. In one embodiment, the

- 16 -

reactor base comprises thermal sensors embedded in the
reactor base and a thermal block that surrounds the
reactor base. The temperature of the thermal block may
be computer controlled. The reactor assembly may be
5   used in conjunction with a dispensing assembly that
dispenses at least one object (e.g., ball or stirring
flea) into a plurality of receptacles located in the
reactor base.

        In another aspect, the filtering assembly
10 includes a reactor base comprising an array of a
plurality of receptacles and a filtration subassembly.
The filtration subassembly includes a plurality of
pairs of holes, where each pair of holes is associated
with a receptacle in the reactor base. One hole may be
15 used for filtering a liquid before it is deposited into
the associated receptacle. The other hole may be used
to provide access to the associated receptacle without
having to pass through a filter. Each pair of holes
may isolated from each other to prevent cross-
20 communication of fluid or vapor among other pairs of
holes. Isolation may be accomplished using o-rings
that are provided in the filtration subassembly. In
particular, the o-rings may be constructed to include a
large o-ring and a small o-ring. The large o-ring may
25 surround each pair of holes to provide inter-pair
isolation. The small o-ring may surround one of the
holes in the pair to provide inter-hole isolation.

        In another aspect, the crystallization
assembly includes a reactor that comprises an optically
30 transmissive substrate. The reactor may include a
plurality of through-holes that correspond to regions

- 17 -

on the substrate. The through-holes may be sealed such
that each through-hole is isolated. In one embodiment,
after the crystals form on the substrate, the substrate
can be removed and subjected to screening test.

5   In another aspect, the invention is directed
toward an apparatus that can determine the melting
point of a crystal or other solid. In one embodiment,
the melting point apparatus includes a thermal chamber
and an image scanning device. An optically

10 transmissive substrate supporting an array of materials
(e.g., crystals) may be contained within the thermal
chamber. The thermal chamber may heat the substrate at
a predetermined rate (e.g., 1° C per minute) to
gradually heat the crystals on the substrate.   As the

15 substrate heats up, the image scanning device provides
an optical signal to each material sample on the
substrate and determines whether the crystal, if any,
melts or changes phase, or whether the crystal changes
composition (i.e., loss of water or solvent molecules).

20   The image scanning device may use
birefringence imaging, light scattering, or other
optical scanning techniques to determine when a crystal
on the substrate melts. Birefringence imaging may be
accomplished using an array of light emitters,

25 polarizer filters and light detectors. In a preferred
embodiment, the image scanning device is computer
controlled. In addition, the computer may also control
the rate in which the temperature of the thermal
chamber is increased. Thus, the combination of

30 temperature and birefringence imaging enables the
present invention to accurately detect the temperature

- 18 -

at which each crystal melts or changes phase, or
whether the crystal changes composition.

In another aspect, the invention is directed
toward hardware and software for controlling various
5   apparatuses associated with the invention. The
hardware and software may control the dispensing of
liquid into the reactor assembly, filtering assembly
and/or crystallization assembly. For example, the
present invention may be able to control an automated
10   pipette system to dispense materials into a reactor
assembly. In one embodiment, the hardware and software
can be integrated with library design software.

Moreover, this invention is directed toward
hardware and software for characterizing and analyzing
15   one or more physical properties of the crystals
obtained during the polymorph characterization or salt
selection methods of the invention. In one embodiment,
the software groups the crystals into families of
compounds based upon similarities in one or more of
20   their physical properties. The physical properties
that are used to group the crystals into families may
be defined by the user and/or may be obtained from
previous characterization experiments. Further, the
different polymorphs or salts may be grouped into
25   families based upon their similarity to one another for
one or more physical properties of interest within a
user-defined deviation. Different families may be
defined by the user based on the same or on different
deviations. The software enables quick analysis of
30   data obtained from screening experiments and provides
for a high throughput methods.

- 19 -

Physical properties that may be used to sort
polymorphs into families include, without limitation,
crystal shape, melting point and spectral properties of
crystals. In a preferred embodiment, the physical
5 property that is used to sort polymorphs into families
is a spectrum of the crystals obtained during the
polymorph characterization. In one embodiment, the
spectra may be obtained by Raman, infrared (IR), near-
IR or X-ray diffraction spectroscopy, wherein the
10 software sorts spectra into polymorph families, and in
some embodiments this sorting is based on pattern
matching. Thus, different polymorphs are grouped into
families based upon their spectral similarities to one
another within a user-defined variation, with different
15 families being defined by the user.

In another aspect, the invention is directed
toward a system for making and characterizing salts
from at least one drug candidate. In one embodiment,
the system may include a computer that controls
20 dispensing, heating, and screening of the materials.
The computer may control robotic equipment to dispense
the drug candidate and one or more acids or bases into
the receptacles to provide the mixture. Once the
mixture is in a reactor assembly, a temperature-
25 controlled housing that houses the reactor assembly may
subject the reactor assembly to a predetermined
temperature to promote dissolution of the drug
candidate contained within the mixture.

Another aspect this invention is directed
30 toward a system that tests a drug candidate in high
throughput mode to make and characterize polymorphs.

- 20 -

In one embodiment, the system includes a reactor
assembly configured to contain a plurality of mixtures.
The system may also include a crystallization assembly
that is configured to contain crystallized compounds on
5 a substrate. In addition, the system may include a
temperature-controlled housing that is configured to
contain an assembly such as, for example, a reactor
assembly, filtration assembly, or a crystallization
assembly and subject the assembly to a predetermined
10 temperature. The system may also include a computer
that controls the temperature-controlled housing and
obtains data from the screening devices. The computer
analyzes the data to determine if any polymorphs have
formed and categorizes the polymorph into the
15 appropriate family.

A further understanding of the nature and
advantages of the present invention may be realized by
reference to the remaining portions of the
specification and the drawings.

20 Brief Description of the Drawings

The above and other objects and advantages of
the invention will be apparent upon consideration of
the following detailed description, taken in
conjunction with the accompanying drawings, in which
25 like reference characters refer to like parts
throughout, and in which:

FIG. 1 shows an illustrative pre-formulation
discovery tool system that is in accordance with the
principles of the present invention;

- 21 -

FIGS. 2A and 2B show an illustrative flow
diagram of salt selection process that is in accordance
with the principles of the present invention;

FIG. 3 shows an illustrative flow diagram of
5 polymorph testing that is in accordance with the
principles of the present invention;

FIG. 4 shows an illustrative library that can
be modeled in accordance with the principles of the
present invention;

10   FIG. 5 shows an illustrative flow diagram of
a library design process in accordance with the
principles of the present invention;

FIG. 6 shows an illustrative flow diagram
that generates a recipe file that enables automatic
15 control of hardware to synthesize a library in
accordance with the principles of the present
invention;

FIG. 7 shows several different crystalline
structures that can be detected with birefringence
20 testing in accordance with the principles of the
present invention;

FIG. 8 shows an illustrative flow diagram for
categorizing samples according to data obtained in
screening tests in accordance with the principles of
25 the present invention;

FIG. 9 shows a graphical representation of
spectral data obtained from a Raman screening device in
accordance with the principles of the present
invention;

30   FIG. 10 shows a graphical representation of
spectral data obtained from a X-ray screening device in

- 22 -

accordance with the principles of the present
invention;

FIG. 11 shows an interactive display screen
that includes several spectral data graphs of
5   crystalline structures discovered in an array of
materials in accordance with the principles of the
present invention;

FIG. 11A shows an illustrative display screen
that enables a user to define parameters used for
10 correlating data in accordance with the principles of
the present invention;

FIG. 11B shows an illustrative display screen
that enables a user to define parameters for preforming
the correlation of data in accordance with the
15 principles of the present invention;

FIG. 11C shows an illustrative display screen
that enables a user associate data with particular
polymorph families in accordance with the principles of
the present invention.

20   FIG. 12 shows an illustrative display screen
that shows the spectral graphs of FIG. 11 in categories
in accordance with the principles of the present
invention;

FIG. 12A shows a flow chart of a process that
25 determines if a material sample should be selected for
additional testing in accordance with the principles of
the present invention;

FIG. 13 shows a cross-sectional view of a
reactor assembly in accordance with the principles of
30 the present invention;

- 23 -

FIG. 14 shows a three-dimensional view of a ball
dispensing assembly in accordance with the principles of
the present invention;

FIG. 14A shows an exploded three-dimensional view
5   of the ball dispensing assembly of FIG. 14 in accordance
with the principles of the present invention;

FIG. 15 shows an exploded view of a reactor
assembly in accordance with the principles of the present
invention;

10   FIG. 16 shows an exploded view of a filtration
assembly in accordance with the principles of the present
invention;

FIG. 17 shows an exploded view of a filter
subassembly of FIG. 16 in accordance with the principles of
15   the present invention;

FIG. 18 shows an embodiment of o-ring sheets that
may be used in the filter subassembly of FIG. 17 in
accordance with the principles of the present invention;

FIG. 19 shows an embodiment of filter disk that
20   can be used in conjunction with the filter assembly of
FIG. 16 in accordance with the principles of the present
invention;

FIGS. 20A and 20B show how a mixture is filtered
using the filter assembly of FIG. 16 in accordance with the
25   principles of the present invention;

FIG. 20C shows how a filtrate is extracted from
the filter assembly of FIG. 16 in accordance with the
principles of the present invention;

FIG. 21 illustrates an exploded view of a
30   crystallization assembly in accordance with the principles
of the present invention;

- 24 -

FIG. 21A illustrates an exploded view of an alternative embodiment of a crystallization assembly in accordance with the principles of the present invention;

5   FIG. 21B illustrates a two-dimensional array of o-rings that are used in conjunction with the crystallization assembly of FIG. 21A in accordance with the principles of the present invention;

FIG. 21C illustrates a partial cross-

10   sectional view of the crystallization assembly of FIG. 21A which in accordance with the principles of the present invention;

FIG. 22 illustrates a partial cross-sectional view of crystallization assembly of FIG. 21 that is in

15   accordance with the principles of the present invention;

FIG. 22A shows an venting needle assembly in an expanded position in accordance with the principles of the present invention;

20   FIG. 22B show a venting needle assembly in a compressed position in accordance with the principles of the present invention;

FIG. 23 shows a process platform that has a liquid handling robot that can dispense and aspirate

25   fluid from assemblies positioned on the platform in accordance with the principles of the present invention;

FIG. 24 shows perspective top and bottom views of a temperature-controlled housing in accordance

30   with the principles of the present invention;

- 25 -

FIG. 25 shows a thermal control chamber in accordance with the principles of the present invention;

FIG. 26 shows a three dimensional view of fluid channels of the temperature-controlled housing of FIG. 25
5   in accordance with the principles of the present invention;

FIG. 27 shows a cross-sectional view of the temperature-controlled housing that includes a crystallization assembly contained within the housing in accordance with the principles of the present invention;

10   FIG. 27A shows a detailed cross-sectional view of the temperature-controlled housing taken along circle 27 of FIG. 27 in accordance with the principles of the present invention;

FIG. 28 shows an apparatus that simultaneously
15   performs melting point and birefringence or light scattering testing in accordance with the principles of the present invention;

FIG. 28A shows an isometric view of the apparatus. of FIG. 28 in accordance with the principles of the present
20   invention;

FIG. 28B shows a cross-sectional view taken along the line 28-28 of the apparatus in FIG. 28A in accordance with the principles of the present invention;

FIGS. 29A, 29B and 29C show Table 3, which lists
25   solvents useful for a process of this invention, including certain physical properties of the solvents that may be used in solvent selection that is in accordance with the principles of the present invention;

- 26 -

FIG. 30 shows an apparatus for performing in-situ measurement in accordance with the principles of the present invention; and

FIG. 31 shows an exemplary crystallization
5   workflow using the methods and apparatus of the invention.

Detailed Description of the Invention

Scientific and technical terms used in connection with the present invention shall have the
10   meanings that are commonly understood by those of ordinary skill in the art with the supplemental definitions found herein, which are not intended to be contrary to the generally accepted definitions. Further, unless otherwise required by context, singular
15   terms shall include pluralities and plural terms shall include the singular.

As discussed herein, an active pharmaceutical ingredient (API) is a specific compound (a salt or a neutral compound) that has been approved by the
20   government for use in a pharmaceutical, e.g., it is safe and effective for a particular indication.

A drug candidate is a precursor to an API. A drug candidate may have shown efficacy under various assays for activity or safety under various toxicity
25   assays. As used herein, a drug candidate is any compound of interest for which pre-formulation testing is desired to determine which form of the compound can or should be prepared. Pre-formulation testing can include salt selection and/or polymorph
30   characterization and analysis. The methodology or

- 27 -

process described in this patent application may be
performed on API's and drug candidates. And, as those
of skill in the art will appreciate, the exact API or
drug candidate is not critical to this invention, but

5   is typically a small molecule (as opposed to a protein)
or a salt thereof. The term drug candidate, as used
herein, refers to a neutral compound or a salt thereof,
unless otherwise specified.

A polymorph of a compound, as used herein, is

10 a crystal of a compound that is able to crystallize in
more than one form. Thus, polymorphs of a compound
refer to different crystalline forms of the compound.
A polymorph may also be a pseudo-polymorph, which is a
crystal of a compound that contains solvent or water

15 molecules (i.e., solvates and hydrates, respectively)
and thus differs from a crystal lacking solvent or
water molecules. As used herein, the term polymorph
refers to both polymorphs or pseudo-polymorphs, unless
otherwise specified.

20   A "crystalline structure," as used herein,
comprises a crystal and a supernatant (or mother
liquor) formed when a solution crystallizes.

The term "solvent" refers to a liquid that is
used to dissolve a drug candidate in the methods

25 described herein. The term "solvent" is also intended
to include mixtures of solvents (i.e., two or more
different liquids that may or may not be miscible).

The term "salt reactant" refers to acids,
bases and salts that are used to produce drug candidate

30 salts. A "salt reactant" may be defined functionally
as a substance that provides an ion (either a cation or

- 28 -

an anion) that forms a salt with a drug candidate.
Generally, a "salt reactant" is added in stoichiometric
amounts to drug candidate, e.g., an approximately equal
number of salt ions of the salt reactant are added as
5   there are acidic or basic moieties on the compound of
interest.

A "salt" is defined as a compound comprising
anions and cations; that is, there is a proton transfer
between the drug candidate and the acid or base. As
10 used herein, a salt complex is a co-crystal of a drug
candidate and a acid or base; that is, there is no
proton transfer between the drug candidate and the acid
or base. Unless indicated otherwise, the term "salt"
as used herein includes both salts and salt complexes.

15   The term "crystallization" or "crystallize"
refers to the process by which crystals form from a
liquid solvent, generating a supernatant (sometimes
referred to as a mother liquor) above the crystals.
Crystallization also refers to a process in which
20 crystals form from melts or sublimation. As used
herein, a "crystal" is a solid in which the molecules
are held together in a regular repeating internal
arrangement.

As used herein, the term "precipitation" or
25 "precipitate" refers to a process by which a solid is
generated by addition of an anti-solvent to a drug
candidate mixture. The solid may be in either
crystalline or amorphous form.

The terms "recrystallization" and
30 "recrystallize" are intended to mean crystallization of
the drug candidate compounds from a solution, without

- 29 -

intending to mean that the drug candidate compounds
were crystals prior to being dissolved, unless
otherwise indicated.

The term "library" as used herein refers to a
5 plurality of experiments, samples or members, wherein
the experiments, samples or members may or may not be
physically associated. Thus, a library refers to
members on a single substrate, on multiple substrates
or on a portion of a substrate. In general, each
10 member will have some data associated with it, which
may include, e.g., drug candidate, salt form, solvent
identity, spectral data, melting point, solubility,
etc.

For purposes of the present invention, the
15 term drug candidate is used generically to represent
material compounds that are being developed and tested
in a process. Further, as used herein, the terms "drug
candidate" or "drug candidate compound" are synonymous
with the term "compound", unless otherwise indicated.
20   The present invention systematically enhances
the efficiency of the pre-formulation process of drug
development. In particular, the pre-formulation
process is implemented as a process that generates,
characterizes and analyzes material compositions. This
25 process can be performed in accordance with the present
invention by using illustrative pre-formulation
discovery tool system 100 shown in FIG. 1. Pre-
formulation system 100 may include computer 110,
material handling apparatus 150, material screening
30 device 160, and user interface equipment 180. Pre-
formulation system 100 may include multiple material

- 30 -

handling apparatuses 150 and multiple material
screening devices 160. Only one each of material
handling device 150 and material screening device 160,
however, is illustrated in FIG. 1 to avoid complicating
5   the drawing. Computer 110 is illustrated to be
connected to apparatus 150, device 160, and user
interface equipment via communication paths 190. In
addition, apparatus 150 and device 160 are also
connected by communication path 190.

10   Computer 110 controls a process that is
implemented to perform the pre-formulation process in
accordance with the principles of the present
invention. Several processes can be implemented in
pre-formulation system 100. For example, a process may
15 be used for creating, analyzing and selecting salts for
a particular drug product. Other processes may be
implemented to generate, characterize and analyze
different crystalline structures (e.g., polymorphs) of
a compound. Comprehensive processes may involve a
20 process that starts with library design of solvents and
ends with identification of a suitable active
pharmaceutical ingredient. Such a comprehensive
process may, for example, combine a salt selection
process with a polymorph process to pre-formulate a
25 desired ingredient. While there are several possible
processes that can be developed and used with pre-
formulation system 110, the present invention
illustrates two such embodiments in FIGS. 2 and 3.

            Computer 110 may include electronic
30 circuitry 112 (e.g., hard-drive, processing memory
communications buses, etc.) that handles transmission

- 31 -

of data to, from, and/or between apparatus 150, device
160, and user interface equipment 180. Electronic
circuitry 112 may enable computer 110 to perform
processes by controlling, for example, apparatus 150

5   and device 160. Computer 110 may initiate processes by
responding to user input from user interface
equipment 180. Computer 110 may also provide
information to the user at user interface equipment 180
with respect to data acquired during operation of the

10 process.

Electronic circuitry 112 may store, retrieve,
and distribute information from database 114.
Database 114 stores information that enables a process
to be created and also provides a basis for performing

15 analysis on a material composition. For example,
database 114 may store information such as method
steps, library designs, results of prior processes,
results of processes in progress, publicly available
data, library compositions, record sets, polymorph

20 family data, and other suitable pre-formulation data.
Database 114 can also store information on material
properties of drug candidates and solvents, such as
molecular weight, density, boiling point, etc. Other
stored information can include recipe files, reagents,

25 solvents, compounds, salts, crystals, polymorphs, all
known characteristics and properties of such materials
and any other information suitable for a pre-
formulation process. Database 114 may be updated with
new information. The new information may be derived

30 from data obtained from a currently active process or
by downloading data via user interface equipment 180.

- 32 -

Computer 110 can run software programs that
assist control and operation of a process. Software
programs may be used to automate pre-determined
portions of the process. For example, software may
5   automate control apparatus 150 in preparing library
compositions. An illustrative example of such software
is Impressionist™ software sold by Symyx Technology,
Inc. of Santa Clara, California. Impressionist™ is
described in WO 00/67086, published November 9, 2000,
10 which hereby incorporated by reference in its entirety.
Other software programs may provide a comprehensive
computer generated library that provide the process
with a template for preparing various material
compositions. A computer generated library
15 advantageously eliminates the time consuming task of
manually determining all the permutations and
combinations of materials that can be compared under a
given set of constraints. An illustrative example of
library design software is sold as Library Studio® of
20 Symyx Technologies, Inc. of Santa Clara, California.
Library Studio® is described in WO 00/23921, published
April 27, 2000, which hereby incorporated by reference
in its entirety. Persons skilled in the art will
appreciate that several software programs may be
25 implemented on computer 110. For example, Epoch™
software sold by Symyx Technologies, Inc. of Santa
Clara, California, may be used to control and acquire
data from instruments such as apparatus 150 and
screening device 160. Epoch™ is described in
30 WO 01/79949, published Octoer 25, 2001, which hereby
incorporated by reference in its entirety.

- 33 -

Material handling apparatus 150 may provide
assemblies that prepare, filter, and/or crystalize
salts or polymorphs of a particular drug candidate in
accordance with the principles of the present
5   invention. Material handling apparatus 150 may be
controlled by computer 110 to automatically mix
specific quantities of material (e.g., drug candidates,
reagents, etc.) to form a material composition. The
materials may be mixed in accordance with library
10 designs produced by computer 110 (e.g., with library
design software). When the materials are mixed, they
may be analyzed by material screening device 160 to
determine various properties such as solubility,
crystallinity, melting point temperature, etc.
15   If desired, material handling apparatus 150
may also be controlled by computer 110 to automate a
crystallization process. For example, computer 110 may
instruct apparatus 150 to subject its resident material
compositions to a precipitation process that causes
20 crystallization. After the crystallization process is
complete, the material compositions are tested for at
least for crystallinity by screening device 160. It
should be noted that above apparatus 150 discussion is
not intended to be exhaustive, rather a detailed
25 discussion of material handling apparatus 150 is
discussed below in conjunction with FIGS. 13-30.
        Automatic control of material handling
apparatus 150 enables the present invention to prepare
several libraries or members. Moreover, automated
30 control reduces possible errors that can be caused by
manual control. In addition, automated control may

- 34 -

enable the present invention to prepare relatively
small sample sizes (e.g., ranging between nanoliter to
milliliter sizes). This advantageously provides high
throughput preparation and testing of the material
5 compositions.

Material screening device 160 analyzes
materials provided on material handling apparatus 150
and provides data to computer 110 based on that
analysis. The analysis of material compositions may
10 also be automated and controlled by computer 110.
Material screening device 160 may include a station
such as, for example, a solubility testing station, a
birefringence station, spectroscopy stations (e.g.,
Raman, infrared, X-ray), a melting point station, an
15 electromagnetic signal absorption (e.g., UV-Vis
absorption) station, partition coefficient (log P)
station, hygroscopicity station, and other suitable
devices. One or more of these stations may provide
data that enables computer 110 to determine the quality
20 and characteristics of a specific material. For
example, computer 110 may determine the quality of a
salt produced based on the characteristics measured by
material screening device 160. In another example,
material screening device 160 may provide data on the
25 crystal structure of a material to computer 110. A
detailed description of several material screening
devices 160 is described below.

User interface equipment 180 enables a user
to input commands to computer 180 via input device 182.
30 Input device 182 may be any suitable device such as,
for example, a conventional keyboard, a wireless

keyboard, a mouse, a touch pad, a trackball, a voice
activated console, or any combination of such devices.
Input device 182 may enable a user to enter commands to
perform drug selection, library building, screening,
5 etc. If desired, input device 182 may enable a user to
control material handling apparatus 150 and material
screening device 160. Using input device 182, for
example, a user may calibrate apparatus 150 prior to
use in a process. In another example, a user may
10 manually control material screening device 160 to
measure materials formulated in material handling
apparatus 150. A user may monitor processes operating
on pre-formulation system 100 on display device 184.
Display device 184 may be a computer monitor, a
15 television, a flat panel display, a liquid crystal
display, a cathode-ray tube (CRT), or any other
suitable display device.

        Communication paths 190 may be any suitable
communications path such as, for example, a cable link,
20 a hard-wired link, a fiber-optic link, an infrared
link, a ribbon-wire link, a blue-tooth link, an analog
communications link, a digital communications link, or
any combination of such links. Communications
paths 190 are configured to enable data transfer
25 between computer 110, apparatus 150, device 160, and
user interface equipment 180. Communications path 190
may also enable data transfer between apparatus 150 and
device 160.

        Various processes can be implemented on pre-
30 formulation system 100. Processes may include several

- 36 -

steps or stages to achieve a desired result (e.g., salt selection, polymorph testing).

Many neutral pharmaceutically active compounds contain functional groups such as amines or
5 carboxylic acids that can react with acids or bases to form salts. In general, salts tend to be more water soluble and have higher melting points than the corresponding neutral compounds. Salt selection for a drug candidate is not necessary if the neutral compound
10 has suitable properties. However, salts of drug candidates often have desirable properties that are useful for formulation or bioavailability. Desirable properties of a salt compared to a neutral compound may include the ability of the salt to form crystals that
15 are produced more easily or cheaply, crystals that are more stable, more filterable, less hygroscopic, more soluble in water, or have a higher melting point or a more favorable log P for administration. For instance, for pharmaceutical compounds listed in the Physicians'
20 Desk Reference (2000) that are salts, more than 50% of the neutral compounds of the salts are insoluble in water (they have a solubility of less than 1 mg/mL). In contrast, less than 20% of the corresponding salts, i.e., the listed pharmaceutical compounds, are
25 similarly insoluble. Further, more than 30% of neutral bases listed in the Physicians' Desk Reference (2000) have a melting point below 120°C, while under 10% of their corresponding salts have a melting point below 120°C. Having a higher melting point is often
30 desirable for easier formulation.

- 37 -

The selection of a salt for a drug candidate
of interest is largely limited to the number of
experiments that can reasonably be performed in the
time allotted. Since the counter-ion affects the
5   physical property of the drug candidate salt, different
salts of the same drug candidate will crystallize under
different conditions and will have different physical
properties. Thus, it is necessary to perform a number
of different recrystallization experiments to generate
10   crystals for different drug candidate salts. By having
a number of different drug candidate salts, one can
identify those salts that are likely to be the most
useful for drug formulation and administration.

Table 1, below, lists common anions for salts
15   and Table 2, below, lists common cations for salts.

Table 1.

Anion	Count	% of Total	Cumulative % of Total	Cumulative % : No. of Compds
Cl	156	60.9	60.9	
SO$_4$	26	10.2	71.1	71% : 2
Mesylate	11	4.3	75.4	
Br	10	3.9	79.3	79% : 4
Tartrate	9	3.5	82.8	
Citrate	8	3.1	85.9	
Maleate	7	2.7	88.7	
Acetate	4	1.6	90.2	90% : 8
Besylate	4	1.6	91.8	
NO3	3	1.2	93.0	
PO4	3	1.2	94.1	
Fumerate	3	1.2	95.3	95% : 12

Succinate	3	1.2	96.5	
Benzoate	1	0.4	96.9	
Gluconate	1	0.4	97.3	
Glucoronate	1	0.4	97.7	
Lactate	1	0.4	98.0	
methylsulfate	1	0.4	98.4	
Oleate	1	0.4	98.8	
Napsylate	1	0.4	99.2	99% : 20
Tannate	1	0.4	99.6	
Xinafoate	1	0.4	100.0	
Total	256		100.0	

Table 2

Cation	Count	% of Total	Cumulative % of Total	Cumulative % : No. of Compds
Sodium	57	76.0	76.0	
Potassium	5	6.7	82.7	83 : 2
Calcium	4	5.3	88.0	
Magnesium	1	1.3	89.3	89 : 4
Ammonium	1	1.3	90.7	
Tromethamine	1	1.3	92.0	
t-Butylamine	1	1.3	93.3	
Piperazine	1	1.3	94.7	95 : 8
Silver	1	1.3	96.0	
Zinc	1	1.3	97.3	
Lithium	1	1.3	98.7	
Gold	1	1.3	100.0	100 : 12
Total	75			

- 39 -

In Tables 1 and 2, the count number and
percent of total indicate the number of drugs and the
percentage of the total that a particular anion or
cation was used as part of an active pharmaceutical
5   ingredient, based on a survey of compounds in use from
the Physicians' Desk Reference (2000). The cumulative
percent of the ions is shown in the fourth column.
Thus, as shown in Table 1, the two most common anions
of active ingredients are chlorides and sulfates,
10 accounting for over 70% of the drugs on the market as
of the printing of the 2000 Physician's Desk Reference
(PDR). This is highlighted further in the fifth
column, which shows that the top two anions account for
71% of drugs on the market at that time, the top four
15 account for 79%, the top eight 90%, and the top twelve
95%. As shown in Table 2, the two most common cations
of API's are sodium and potassium, accounting for over
80% of the drugs on the market at the time. For
cations, the top two cations account for 83% of drugs
20 on the market at the time, the top four account for
89%, and the top eight account for 95%. With the
combinatorial or high throughput techniques of this
invention, both anionic and cationic salts can be
screened, such that for most drug candidates, most if
25 not all commonly used pharmaceutically useful salts can
be tested.

In some embodiments of this invention, at
least two, four or six different salt forms of one or
more drug candidates are produced and screened for
30 desired properties. In other embodiments, at least
eight, more specifically at least 10, at least 12, at

- 40 -

least 16, at least 20, or at least 24 different salt
forms of one or more drug candidates are produced and
screened for desired properties. In one embodiment,
salt reactants comprising the two, four, six or eight
5 most common anions or cations, as shown in Tables 1 and
2, are used for screening. In another embodiment, high
throughput screening is performed using salt reactants
for both anions and cations. Thus, salt reactants for
the two, four, six or eight most common anions and
10 cations are used.

The number of solvents that may be used for
salt selection may be any number desired. In one
embodiment, the number of solvents is two four, six,
eight, 12, 16 or more. The screening of salt and
15 solvent combinations (discussed below) can be at the
rate of at least eight at a time, at least 12 at a
time, at least 24 at a time, at least 36 at a time, at
least 48 at a time, or at least 96 at a time.
Depending on how the library is designed, there can be
20 different salts in a plurality of wells; alternatively,
there can be different solvents in a plurality of
wells, etc.

In one embodiment, a different salt is
present in each row of a substrate, wherein a row
25 comprises a number of wells. The substrate may be a
microtiter plate or another substrate on which wells
may be formed, e.g., using the salt reaction apparatus
described herein. Each column, which also comprises a
number of wells and is perpendicular to the row
30 containing the salt, contains a different solvent.
See, e.g., FIG. 15, which shows an example of a

- 41 -

microtiter format containing rows and columns. The
library is not limited in this manner. This rate of
testing allows for rapid discovery of the appropriate
salt(s) for further investigation.

5   FIGS. 2A and 2B show an illustrative flow
diagram of salt selection process 200 which is in
accordance with the principles of the present
invention. Generally, process 200 dispenses a drug
candidate compound in a receptacle in an array format
10 (e.g., an 8 by 12 array) and subjects each drug
candidate to various combinations of one or more salt
reactants and, optionally, a solvent. In one
embodiment, each receptacle contains at least one drug
candidate, a stoichiometric amount of at least one salt
15 reactant, and, optionally, a solvent. In a preferred
embodiment, each receptacle contains one drug
candidate, a stoichiometric amount of one salt reactant
and a solvent. Depending on the interaction of mixture
of the drug candidate, salt reactant and solvent, a
20 salt may form and precipitate or crystallize. Salts
may then be screened and analyzed to determine whether
the properties and characteristics are suitable for a
particular drug application.

             Processing selected drug candidates or salts
25 for discovery and characterization required at least
two, but preferably at least three steps that are
performed in a combinatorial or high throughput mode.
One required step is dissolution of drug candidates or
salts to form a solution. Another required step is
30 crystallization (e.g., by evaporation, cooling or
precipitation with an anti-solvent) of drug candidates

- 42 -

or salts from the solution. An optional processing
step prior to crystallization may include separating
any remaining solids from the solution by filtration or
centrifugation. This separation or filtering step may
5   be performed to eliminate nucleation sites in the
solvent provided to the crystallization step.
Process 200 includes the preparation, crystallization,
filtration, and other steps that are performed for salt
selection.

10   Prior to preparing solutions comprising the
drug candidate and the salt reactant, a user may
interact with a computer (e.g., computer 110 of FIG. 1)
to generate a model library. At step 210, one or more
computer generated libraries are generated to enable
15   process 200 to prepare substantially every possible
combination of materials that can be mixed within a
given set of constraints. Thus, when these mixtures
are prepared and then crystallized, the present
invention can determine which mixture provides the best
20   salt. Each individual mixture is commonly referred to
as a library member or member. The computer generated
model library may be generated using a number of
parameters (also called constraints) that typically
include materials such as drug candidates, salt
25   reactants, solvents, environmental conditions, reaction
parameters, etc. Parameters may be selected by a user
or a software program. Preferably, a user selects one
or more drug candidates for modeling in the library and
other parameters such as library size (e.g., a 96 well
30   array). A library member usually comprises a drug
candidate, a salt reactant and a solvent. The solvent,

- 43 -

referred to as a library solvent in method 200, is used
for crystallizing the salt produced by the reaction of
the salt reactant and the drug candidate. Computer
generated library designs are preferably modeled by
5   software programs running on computer 110 (shown in
FIG. 1). The computer generated library may be based
on user input and information available from
database 114. The computer generated library is
described in more detail in conjunction with FIGS. 4
10   and 5.

        Persons skilled in the art will appreciate
that computer need not be used to prepare a library. A
person could manually prepare a library using any
suitable method.

15   At step 212, a drug candidate and a salt
reactant are mixed together. An optional mixing
solvent, which may be different or the same as the
library solvent, may be added to the salt reactant and
drug candidate. The drug candidates, salt reactants
20   and optional mixing solvents are reacted together to
produce drug candidate salts. At optional step 214,
after the drug candidate salts have been produced, the
drug candidate salts are isolated. At step 216, the
library solvents provided at step 210 are added to the
25   drug candidate salts to produce the library members.

        In a preferred embodiment, the drug candidate
mixture described at step 212 is prepared in a reactor
assembly. Reactor assemblies are typically constructed
in microtiter format (e.g., an 8 x 12 96-well plate).
30   Microtiter format is particular useful for performing
high throughput reaction of materials. However, any

- 44 -

other format may be used (e.g., a 384 well plate). In
addition, this enables process 200 to construct a
library in reactor assembly 1300 in accordance with the
computer generated library provided at step 210.

5   At step 212, drug candidates may be mixed with
salt reactants according to the computer generated
library at step 210. The mixture may optionally
comprise one or more mixing solvents to provide a salt
solution. The drug candidate is typically dispensed

10 (into reaction containers) as a solution or a slurry,
but it can be also be dispensed as solid. A liquid
dispensing device is illustrated in FIG. 23. A solid
dispensing device (not shown), for example, is sold as
Powdernium by AutoDose of Geneva, Switzerland.

15 Assuming that the drug candidate is in a solution or
slurry, the solvent may or may not be driven off across
the plate in parallel (such as by blowing nitrogen over
the library or with a solvent evaporator, e.g., Genevac
HT-8 (Genevac Inc, Valley Cottage, NY 10989) under

20 reduced pressure or vacuum. If the drug candidate is
dispensed in the reaction solvent, then solvent removal
is unnecessary.

        After dispensing of the drug candidate, the
chosen salt reactant (e.g., an acid or base in

25 solution, slurry or solid format) is dispensed into the
wells of the array. For anion salts, the corresponding
acid is used. For example, hydrochloric acid, sulfuric
acid, mesylic acid and bromic acid may be used for
chloride, sulfate, mesylate and bromate salts of

30 compounds. For cationic salts, one may use the
corresponding hydroxide or other base. For instance

- 45 -

sodium hydroxide and potassium hydroxide may be used for sodium and potassium salts. Magnesium and calcium salts of drug candidates may be formed by using magnesium or calcium acetate, oxide or carbonate.

5   Amine salts may be formed by mixing the amine of choice itself with the drug candidate. In one embodiment, the salt reactant is dispensed automatically into the wells of the array, as discussed in more detail below. In another embodiment, the salt reactant is dispensed

10 manually into the wells of the array.

The salt solution is subjected to various conditions to allow the drug candidate to react with the salt reactant under the conditions imposed. Common reaction conditions are a temperature of about room

15 temperature or higher with shaking in sealed vials. The temperature may be approximately 20°C, 30°C, 40°C, 50°C, 60°C, 70°C, 80°C or higher. In one embodiment, the temperature is raised to approximately 70°C to allow the drug candidate to react with the acid or

20 base. Depending on the drug candidate and the salt reactant, a reaction between the drug candidate and the reaction solvents may or may not occur.

Individual vials or wells may contain magnetic stirring fleas that are tumbled (e.g.,

25 rotated) by a magnetic field or a rotating magnet. The rotating stirring fleas promote mixing of the materials contained within the vials or wells. A detailed explanation of a device that provides magnetic stirring is described in United States Patent 6,176,609, which

30 is hereby incorporated by reference in its entirety.

- 46 -

At optional step 214, after each library member is prepared, any remaining salt reactants and optional solvents are removed from the reaction mixture. This may be done by any method known in the
5 art, including, e.g., methods used for crystallization, such as evaporation, cooling or addition of an anti-solvent.

At step 216, one or more library solvents are added to each well in accordance with the computer
10 generated library and the drug candidate is dissolved in the solvent.

At optional step 220, after each library member is prepared, an aliquot of the salt solution is taken from each reaction container and filtered by a
15 filtration assembly. Each salt solution is filtered so that a "seedless" salt solution is used for crystallization at step 222. FIGS. 16-20 illustrate various filtration apparatuses that provide filtration in accordance with the principles of the present
20 invention.

If seeding is desired, a seed may be added separately, so that seeded recrystallization is controlled.

At step 222, the filtered salt solutions are
25 crystallized. Salt crystallization can occur by 1) cooling the solution, 2) precipitating the solution by adding an anti-solvent that causes precipitation, 3) evaporating the solution, or 4) slurrying the solution. If salt crystallization or precipitation occurs on a
30 multi-well plate or a substrate, such as the universal substrate described herein, the plate or substrate may

be screened by various identifying and characterization devices. If desired, characterization can be performed while recrystallization is occurring. The salt reactants and solvents that may be used to crystallize

5   or precipitate the salts are described below in solvent selection section.

Each library member is screened to determine if a salt has formed. Screening is performed at step 225 and can be implemented using material

10   screening device 160 (shown in FIG. 1). Screening at step 225 may be performed primarily as a high-throughput screen that quickly characterizes each library member. Data obtained during the screening may be provided to a computer (e.g., computer 110). For

15   example, screening at step 225 may obtain a sufficient quantity of data on each library member such that process 200 can be used to quickly analyze the salt. The apparatus and methods described herein provide several screening methods and devices that can

20   determine birefringence, log P, crystallinity, solubility, and melting point of each library member *in situ*.

At step 230, process 200 can perform a quick preliminary assessment on the suitability of each salt

25   before additional time consuming tests are performed. Analysis can include user-defined selection by selecting which library members should be explored further. Salt selection can also be performed, for example, by computer. A computer can run software

30   programs that analyze the data. For example, results of the screening can provide information regarding

- 48 -

whether the salt formed a solid, whether the solid was
amorphous or crystalline, and information regarding the
solubility, log P and melting point of the crystal.

At step 240, process 200 determines if a salt
5 should be selected for further testing or if it should
be discarded. If none of the salts produced in the
library are suitable for additional testing (e.g.,
screening), the process returns to step 212 so that new
library compositions can be prepared. The data
10 obtained from these salts, however, is stored on a
database and used for future analysis. Preferably,
process 200 continues to prepare library compositions
based on computer generated library models generated in
step 210. However, if step 240 determines that there
15 is at least one suitable salt, process continues to
step 250.

At step 250 in FIG. 2B, the salt selected in
step 240 is resynthesized in bulk format. This step is
only necessary if sufficient quantities of the salt
20 selected in step 240 were not produced. In step 250,
multiple samples of the same material composition are
deposited in a different reactor assembly. If desired,
additional solvents may be applied to the existing
library compositions to obtain, for example, additional
25 salt characteristics. The application of new materials
may be based on a library modeled at computer 110
(FIG. 1). Then the newly-formulated library
compositions are crystallized to form salt.

At step 255, the salts are screened again to
30 obtain property and characteristics data, if more data
are required. This screening can be used to provide a

- 49 -

more in-depth characterization of the salts than
screening step 225. Step 255 obtains data that enables
process 200 to perform a secondary analysis (shown at
step 260). At step 260, a substantial analysis may be
5   performed using the data provided by step 255. At
step 270, process 200 determines if the salt should be
selected for further testing. If the salt is not
selected, process 200 may return to step 212 (FIG. 2A).
If the salt is selected, then process 200 has
10   discovered a salt that is suitable for use in another
application. Persons skilled in the art will
appreciate that one or more salt forms may be selected
by process 200 and it will also be appreciated that
process 200 may not produce any salts that are selected
15   based on the parameters set in step 210.

         If desired, after a salt is selected
process 200 may proceed to step 310 of FIG. 3. As
described below, FIG. 3 describes polymorph generation
and characterization based on the selected salt.
20   Process 200 may be implemented on pre-
formulation system 100 to select salts that are
suitable for drug development. Process 200 may be used
as precursor to another process that performs test on
one or more selected salts to determine various
25   potential polymorphs of the salt's crystalline
structure. Persons skilled in the art will appreciate
that steps shown in FIG. 2 are merely exemplary and
that additional steps may be added and some steps may
be omitted or modified. For example, a step can be
30   added that causes process 200 to prepare and test every
library member provided by the computer generated

- 50 -

library in step 210 even if one or more suitable salts
have been discovered. Further, daughter libraries may
be formed to alter the conditions under which salts may
be formed (e.g., temperature or temperature ramp rate)
5   or to provide identical salts for destructive analyses
(e.g., melting point screens).

FIG. 3 shows an illustrative flow diagram of
polymorph discovery process 300 which is in accordance
with the principles of the present invention.
10 Process 300 may be implemented on pre-formulation
system 100 independent of other processes or it may be
merged with processes such as process 200 of FIGS. 2A
and 2B.

Process 300 recrystallizes one or more drug
15 candidates or salts (i.e., subjecting them to different
conditions to generate as many polymorphs as possible,
preferably substantially every polymorph, for a
particular drug candidate or salt thereof) and screens
each of the polymorphs in a high-throughput capacity.
20 This enables process 300 to quickly characterize and
determine those recrystallization conditions that are
best for developing a desired drug ingredient that
possesses a suitable crystalline structure. As used
herein, recrystallization and crystallization
25 conditions refer to those conditions that affect
recrystallization. These conditions include, e.g.,
temperature, seeding (if present), solvent(s), etc.

Process 300 begins at step 310. At step 310,
process 300 is provided with one or more drug candidate
30 salts (or neutral compounds) for polymorph testing.
The drug candidates can be preselected, for example, by

- 51 -

a user via user interface equipment 180 (shown in
FIG. 1). Drug candidates may also be provided by salts
selected in process 200 of FIGS. 2A and 2B.
Alternatively, step 310 may be provided with one or
5 more drug candidates that can be used for polymorph
testing.

Once a drug candidate is provided at
step 310, the drug candidate may undergo
recrystallization at step 320. If desired,
10 recrystallization may involve several steps to form
crystals from a particular drug candidate. For
example, after a drug candidate has been selected, it
may be mixed with solvents 322 in a reaction assembly
(e.g., reaction assembly 1300 of FIG. 13 or reaction
15 assembly 1500 of FIG. 15). The drug candidate and
solvents may be dispensed into a reaction assembly
using a liquid dispensing assembly as described for
salt selection process 200. The solvents may be mixed
in accordance with a computer generated library 321 to
20 provide as many different crystallization mixtures for
a particular set of constraints. Solvent selection is
described further below.

The number of solvents that may be used for
polymorph generation and characterization may be any
25 number desired. In one embodiment, the number of
solvents is two, four, six, eight, 12, 16, 24, 36, 48,
96 or more. The number of solvents that may be used
for polymorph generation and characterization for a
single assay can be at the rate of at least eight to
30 ten at a time, at least 12 to 14 at a time, at least 24
at a time, at least 36 at a time, at least 48 at a

- 52 -

time, or at least 96 at a time. The term solvent in
this respect means both a single solvent (e.g., heptane
or water) as well as combinations of solvents (e.g.,
heptane mixed with water), as described herein.

5   In one embodiment of this invention, at least
one drug candidate is used in a process of generating
and characterizing polymorphs. In other embodiments at
least two, three or four drug candidates are used to
generate and characterize polymorphs.

10   If further desired, recrystallization may
include filtering the mixtures to provide "seedless" or
"pure" solutions for crystallization. A filtering step
is performed formulation and prior to crystallization.
Crystallizing filtered solutions eliminates nucleation

15 sites that can bias formation of crystals during the
crystallization step. Filtering may be accomplished
using filtration assembly 1600 of FIG. 16.

             Various recrystallization conditions (e.g.,
temperature, pressure, time, etc.) may be varied to

20 provide various crystal formation. FIGS. 21 and 22
illustrate, for example, an apparatus that can be used
to crystallize the mixtures. One advantage of this
apparatus (e.g., crystallization assembly 2100 of
FIG. 21) is that crystals may grow, form or re-salt on

25 a removable substrate. This substrate may be provided
to one or more screening devices such that crystals are
scanned for their properties and characteristics at
step 330.

             To perform crystallization or
30 recrystallization under a variety of crystallization
conditions, daughter libraries may be created from

- 53 -

drug candidates, mixtures, or salts thereof. A
daughter library is created by taking one or more
aliquots from one or more members in a parent library
contained within a reactor assembly. A parent library
5   may include mixtures that are prepared at the beginning
of recrystallization step 320. An aliquot is a
definite fraction of a whole.

        To perform daughtering, a pipette, operated
either manually or automatically (e.g., robotically),
10   draws a portion of a member from the parent library and
dispenses that aliquot into another container (e.g.,
crystallization assembly) to provide a daughter library
member. A limited number of members of the parent
library may be daughtered or all the members may be
15   daughtered at least once to create a daughter library.
Thus, a daughter library may be smaller than the parent
library in terms of either mass, volume or moles and/or
in terms of the number of members. Daughtering is
performed, for example, to allow for multiple
20   experiments on identical mixtures, solutions, or
samples to avoid having to recreate the parent library.
There is known equipment that can perform daughtering,
such as hand pipetters, hand-multichannel pipetters, or
robots (such as Matrix or CyberLab or Hydra robots).
25   Any number of daughter libraries may be produced,
provided that the original library is of sufficient
volume. In one embodiment, at least one, two, four,
eight or twelve daughter libraries are produced.

        After the mixtures from the parent library
30   and daughter libraries are crystallized, each library
member is screened. Step 330 provides primary

- 54 -

screening that provides data to step 335, which
analyzes the data to determine if any polymorphs have
formed.

The crystals may be screened for any physical
5   property that would help characterize and/or identify a
polymorph. The crystals may be screened for
birefringence, melting point, solubility,
hygroscopicity, IR pattern, Near IR pattern or Raman
pattern, crystal morphology, X-ray powder diffraction
10 pattern or any other suitable screening method to
determine if crystals (or polymorphs) have formed. In
general, at least two properties are screened. In one
embodiment, Raman pattern, X-ray diffraction pattern,
melting point, birefringence and hygroscopicity screens
15 are performed to adequately characterize the
crystalline structures.

At step 340, process 300 determines whether a
polymorph should be selected being produced in bulk for
further testing, if sufficient quantities of the drug
20 candidate have not been produced during process 300.
If the polymorph is unsuitable, the process may revert
back to step 320 such that the same or different drug
candidates can undergo recrystallization. If the
polymorph is selected, process 300 may prepare several
25 of the same crystals at step 345 so that they can be
screened and characterized at step 350.

At step 350, the screening is more detailed
than the screening performed at step 330. The crystals
may be screened for at least two properties, three
30 properties, four properties or five properties to
identify and characterize polymorphs, wherein the

- 55 -

properties are determined by, e.g., birefringence,
melting point, solubility, hygroscopicity, IR pattern,
Near_IR pattern, Raman pattern, crystal morphology or
X-ray powder diffraction pattern or, if sufficient
5   amounts have been produced, single crystal X-ray
diffraction, thermogravimetric analysis, nuclear
magnetic resonance or differential scanning
calorimetry. In one embodiment, the crystals are
screened for at least birefringence, melting point,
10   solubility, Raman pattern and X-ray powder diffraction
pattern. Preferred embodiments include Raman and/or X-
ray diffraction spectroscopy. The process may be
performed using a solubility testing station, a
birefringence station, spectroscopy stations (e.g.,
15   Raman, infrared, X-ray), a melting point station, an
electromagnetic signal absorption (e.g., UV-Vis
absorption) station, partition coefficient (log P)
station, using the apparatus described herein.

The data obtained in step 350 may provide a
20   substantial quantity of information to enable process
300 to analyze the polymorphs or crystalline structures
(step 360). At step 365, process 300 may determine if
the polymorph (e.g., neutral drug candidate compound or
salt thereof) is suitable for use as an active
25   pharmaceutical ingredient (step 370). If the polymorph
is not suitable, then that particular drug candidate is
not used, at least for the drug application prescribed
for process 300 (step 375). The data obtained from
analysis, however, may be stored for future reference.

30   As illustrated in FIGS. 2A, 2B, and 3,
processes use computer generated libraries as a

- 56 -

template for preparing library members. For example,
libraries containing various combinations of drug
candidates, salts, crystals, and other pre-formulation
materials may be generated prior to library
5 preparation. FIG. 4 shows an illustrative library 400
that can be generated in accordance with the principles
of the present invention. Library 400 can include any
suitable number of library elements 410. Preferably
the number of library elements modeled in each
10 library 400 is the same as the number of library
members 410 that can be prepared on hardware (e.g., a
substrate). Any number of rows and columns of library
members 410 can be created, thus providing flexibility
in library generation. This is illustrated by the
15 variable "N", which indicates that any suitable number
of rows and columns can be designed in library 400.
The row may, for example be Industry typically uses a
substrate that has 96 wells or vials for formulating or
mixing various materials. Therefore, if library 400 is
20 modeled to have, for example, eight rows and twelve
columns (a typical microtiter plate), library elements
410 may be readily implemented in practice. Likewise,
if a 384 well substrate is being used, then library 400
may be modeled to have, for example, 16 rows and 24
25 columns.

        Regardless of the size of library 400, each
library element 410 includes at least two materials.
The materials in each library element 410 can differ by
drug candidates, different known crystal structures of
30 drug candidates, solvents and salt reactants. FIG. 4
shows a few example materials 420 that can be used to

- 57 -

model library elements 410. Based on materials 420 and
other factors, a computer (e.g., computer 110 of
FIG._1) can model substantially every possible
combination of library elements that can be practically
5   constructed. For example, library element 411
illustrates one such possible combination that includes
a drug candidate, the salt reactant tartaric acid, and
heptane. Thus, generating libraries provides the
present invention with a foundation to prepare and test
10   several different material compositions. This
facilitates salt selection and provides a basis for
discovering polymorphs for a particular drug candidate.

A large number of solvents are known that can
be used in recrystallization, either for salt selection
15   and/or for polymorph generation. Table 3 (shown in
Figures 29A, 29B and 29C) lists a number of exemplary
solvents along with some of their physical properties.
Given the large number of solvents that may be used, it
is advantageous to cluster solvents into groups based
20   upon certain shared physical properties or other shared
characteristics of the solvents and then pick at least
one solvent from each group to test in
recrystallization. This process ensures that a wide
variety of different types of solvents will be used for
25   recrystallization, which is advantageous for
identifying polymorphs or desirable crystals of drug
candidate salts.

Table 3 shows solvents along with their
chemical class, a reference number (#) assigned to
30   different classes of solvents (for statistical sort
purposes), molecular weight (MW), density (n), molar

volume (V_m), melting point (MP) (in °C), boiling point
(BP) (in °C), enthalpy of evaporation (ΔH_{vap}),
Hildebrand solubility parameter (δ), dipole moment (μ),
log solubility in water (log S), partition coefficient

5   (log P), viscosity, index of refraction, pKa (in water
and dimethylsulfoxide (DMSO)), dielectric constant (ϵ)
and ionization potential (IE) and pK_{a+}. Other
parameters known to those in the art could be included,
such as, without limitation, the cost in US dollars per

10   kilogram, cost of disposal or storage, degree of
toxicity or environmental safety. The description of
the solvents and physical properties provided herein
does not limit the type of solvent or the physical
properties of the solvent that may be used in the salt

15   selection and polymorph workflows.

One or more of the physical properties of the
solvents in a solvent library may be used to cluster
solvents into groups. The solvents in a particular
group will have similar physical properties for the one

20   or more properties that has been chosen as a criteria.
The physical properties of the solvents may be one or
more of those listed in Table 3 or may be other
physical properties known in the art. One may use from
one to n properties to cluster the solvents into

25   groups, wherein n is the total number of physical
properties that have been provided for a library of
solvents. Each solvent may be independently sorted
into a group with other solvents that have the same
defined characteristics for all of the selected

30   physical properties. One may use any number of
properties to cluster solvents, including from four to

20, four to 16 or six to eight properties to cluster the solvents. In one embodiment, the class of the solvent (e.g., whether it is an alcohol, ketone, etc.) is not employed as one of the physical properties used 5 in grouping the solvents.

For any particular physical property, the selection criteria may be defined to provide for two or more different subsets. In one embodiment, the selection criteria for single physical property 10 solvents may provide for two, four, six, eight or twelve subsets. For example, one may provide four definitions for dividing the solvents based upon one physical property (e.g., the solvent's density) and provide two definitions for dividing the solvents based 15 upon another physical property (e.g., the solvent's dipole moment). The solvents would then be clustered into eight groups based upon the definitions of these two physical properties.

In a preferred embodiment, the physical 20 properties of a large number of solvents are kept in a database. During library design for polymorph generation or salt selection, a user can define both the specific physical properties and the selection criteria for these physical properties in order to 25 cluster the solvents into groups based upon the particular physical properties chosen and the selection criteria for these physical properties.

One may design solvent groups to form from two groups up to n groups, wherein n is the total 30 number of solvents in the designated solvent library. In one embodiment, the number of solvent groups is four

- 60 -

to 96 groups. In another embodiment, the number of
solvent groups is six to 64, eight to 48 groups, ten to
40 groups or 12 to 24 groups. In another embodiment,
the number of solvent groups is eight to 24 groups, 16
5   to 24 groups, 20 to 40 groups or eight to 12 groups.
In general, a smaller number of solvent groups are used
for the salt selection workflow as compared to the
polymorph characterization workflow. For salt
selection, the number of solvent groups is generally in
10 the range of 16 to 24 groups, while for polymorph
identification and characterization, the number of
solvent groups is generally around 20 to 40.

In one embodiment, in order to provide
diversity of the types of solvents that are used for
15 salt selection or polymorph generation, a solvent
library may be clustered into groups of solvents having
particular similar physical properties or
characteristics and at least one solvent from each
group is used in the salt selection or polymorph
20 generation. In another embodiment, a number of
solvents from a single group may be selected and used
in salt selection or in polymorph generation. This may
be particularly useful at later stages in polymorph
characterization, to identify potential facile, stable
25 or commercial methods for generating a particular
polymorph for an active pharmaceutical ingredient, or
to prepare focused solvent libraries.

Solvent group design may be performed by any
method known in the art, including manual design or
30 computer design. Commercially available computer

- 61 -

programs can be used, including JMP™, available from
SAS Institute, Inc., Cary, North Carolina.

In general, solvents are chosen to have a
boiling point higher than the temperature at which the
5   crystallization will be run. Other physical properties
that are preferred are those in which non-toxic
solvents are used. In another embodiment, one or more
solvents such as ethanol, water, cyclohexane, propanol,
acetonitrile, dioxane, methyl ethyl ketone, ethyl
10 acetate, isopropyl acetate, propyl acetate or toluene
are used as a solvent in the methods described herein.

In one embodiment of a salt selection array,
one axis of the array (e.g., the rows of a microtiter
plate or other substrate) contains a constant amount of
15 the drug candidate of interest mixed with a number of
different salt reactants, wherein each row of the array
contains a different salt reactant. In general, the
drug candidate is mixed with one equivalent of the salt
reactant (e.g., an acid or base). However, in another
20 embodiment, the drug candidate may be mixed with 0.5,
two, 1.5, three or four equivalents of the salt
reactant.

The opposite axis of the array (e.g., the
columns of the microtiter plate) contains a number of
25 different solvents, wherein each column of the array
contains a different solvent. In a preferred
embodiment, the solvents have been clustered as
described herein. Thus, each well of the array
contains a different combination of salt reactant and
30 solvent.

- 62 -

The salt reactant and drug candidate may be subjected to conditions in which a salt may form prior to addition of the solvent, e.g., by heating, stirring, shaking or any combination thereof. An array of
5 solvents may then be added and the presence of crystals or precipitates of drug candidate salts may be determined. Alternatively, the drug candidate, salt reactant and solvent may be mixed together prior to subjecting the array to conditions under which a drug
10 candidate salt and crystal or precipitate thereof may form. In one embodiment, the array can be subjected to salt synthesis and crystallization using one or more of the apparatus described herein.

In another embodiment, one axis of the array
15 (e.g., the row) contains the drug candidate of interest mixed with a number of different salt reactants while the opposite axis (e.g., the column) contains solvents or compositions of two or more solvents, wherein each column contains a different solvent or solvent
20 composition. In one embodiment, the solvent compositions in the array or part thereof may be different concentrations of the two solvents relative to each other. The concentrations of the solvents relative to one another may be any concentration
25 desired. In one embodiment, an array of solvent compositions (e.g., gradient) for solvents A and B can be expressed in the following formula:

$$x * A (100 - x) * B = 0 \qquad (1)$$

where x is the percentage.

30 If desired the gradient can be determined using a linear function, a non-linear function, a

polynomial function, an exponential function, etc. For instance, one may vary the concentration of water and heptane in this manner. Similarly, an array of solvent compositions using three, four or more different

5 solvents may be produced, wherein the relative concentrations of the solvents to each other are varied in the array. In a preferred embodiment, the solvents in the solvent composition have been clustered as described herein. As discussed above, the array can

10 then be subjected to conditions in which drug candidate salts would likely form crystals.

A single drug candidate (either a salt or a neutral compound) is typically tested for polymorph generation and characterization, although two, four,

15 six, eight or more may also be characterized. Because different drug candidate salts do not have to be formed, more solvents are typically used for polymorph generation and characterization than is typical for salt selection. However, except for the larger number

20 of solvents that are generally used, solvent group selection for polymorph generation and characterization is similar to that for salt selection. Thus, in one embodiment, a library of solvents may be divided into more groups for recrystallization compared to that for

25 salt selection, while in another embodiment, more solvents within a single group may be used to recrystallize a drug candidate salt.

In one embodiment of a polymorph array, each well contains a constant amount of the drug candidate

30 of interest and a different solvent. The solvents may be selected by any method known in the art. For

- 64 -

example, the solvents may be selected from different
industrially important categories of solvents,
including aromatics, ketones, water, halogenates,
alcohols, esters, nitriles, as well as solvent mixtures
5   that span a wide range of polarity and dielectric
constant. In a preferred embodiment, the solvents are
selected by the solvent selection method described
previously, by dividing a library of solvents into
groups based upon a variety of different physical
10   properties or characteristics. More preferably, the
solvents are not selected based upon their chemical
class. After the solvent has been added to the drug
candidate, they are mixed under conditions to dissolve
the drug candidate, optionally filtered, and then
15   subjected to conditions in which crystals are likely to
form.

Using an array of different types of
solvents, whether based upon the chemical class or
their physical properties, provides a large amount of
20   information regarding which types of solvents
recrystallize the drug candidate. Further, using a
wide variety of solvents is likely to provide a large
number of different polymorphs of the crystalline drug
candidate, if they exist. See, e.g., FIG. 7, which
25   shows changes in crystal morphology of a drug candidate
after crystallization from different solvents. These
solvents included those that are miscible in heptane
and those that are miscible in water. Once one or more
solvents have been identified that recrystallize the
30   drug candidate, other solvents that are of the same
chemical class or share physical properties or

- 65 -

characteristics with the identified solvents may be
used in further experiments. These experiments can be
performed to generate and characterize polymorphs of
the drug candidate as well as to find the best
5 recrystallization solvent for the particular drug
candidate.

In another embodiment of a polymorph array,
the array contains the drug candidate of interest mixed
with compositions of two or more solvents, wherein each
10 well contains a different solvent composition. See,
e.g., Example 3. In one embodiment, the solvent
compositions in the array or part thereof may be
different concentrations of the two solvents relative
to each other. The concentrations of the solvents
15 relative to one another may be any concentration
desired. In one embodiment, an array of solvent
compositions for solvents A and B may be determined
using equation 1. Similarly, an array of solvent
compositions using three, four or more different
20 solvents may be produced, wherein the relative
concentrations of the solvents to each other are varied
in the array. In a preferred embodiment, the solvents
in the solvent composition have been clustered as
described herein. As discussed above, the array can
25 then be subjected to conditions in which crystals would
likely be synthesized, and the presence of crystals and
polymorphs can be determined. One can use different
concentrations of solvents to determine at what
concentration a solvent causes the drug candidate to
30 crystallize. In addition, one can use different
concentrations to determine whether different types of

- 66 -

crystals are formed in different concentrations of
solvent.

In another embodiment, solvent group design
may be performed by providing a database containing

5   information associating the physical or chemical
properties of particular solvents with the production
of crystallographic forms of drug candidates,
identifying in the database which physical properties
are associated with producing a large number of

10 crystallographic forms, and designing new libraries
using these identified physical or chemical properties
as criteria for grouping solvents.

FIG. 5 shows an illustrative flow chart of
library design process 500 in accordance with the

15 principles of the present invention. Library design
process 500 may be used, for example, to generate
library 400 illustrated in FIG. 4. At step 510, a user
may define or select one or more sources using a user
terminal (e.g., user interface equipment 180 of

20 FIG. 1). Sources may include materials such as salt
reactants, solvents, drug candidates, mixtures of
solvents, etc. that are used to prepare a library.
Also at step 510, a user may define or select a library
layout. A library layout may represent the layout in

25 which a library will be created on a substrate (e.g,. a
substrate with an 12 by 8 matrix array of wells) or a
reactor assembly. Alternatively, a library layout is
not necessarily confined to actual physical parameters,
rather it can be provided in an intangible format

30 (e.g., on a computer).

- 67 -

The user can identify source materials and
library layouts by entering identifying information
manually or by selecting identifying information from a
pre-defined source such as database 114 of FIG. 1.

5   At step 520, process 500 may define the
composition of each library member based on the sources
selected in step 510. The composition of each library
member is defined by a mapping sequence that assigns
materials to each library member. The mapping sequence

10   may be automatically generated or defined by a user.
Automatically generated mapping sequences may provide
an exhaustive mapping of material compositions than can
be used to create libraries.

When step 520 has completed defining the

15   composition of each library member, process 500
optionally proceeds to step 530. At step 530, a recipe
file is generated based on the composition defined at
step 520. The recipe file may embody handling
instructions that can enable instruments such as

20   material handling apparatus 150 (FIG. 1) to prepare
the library. Step 530 is optional because the library
mapping parameters can be integrated with software that
controls a material dispensing apparatus to prepare
members of substrate according to the library.

25   Persons skilled in the art will appreciate
that the above discussion with respect to FIGS. 4 and 5
is not intended to be an exhaustive description of
library designing. The discussion does, however,
discuss a portion of the various features pertinent to

30   describing the present invention. For example,

- 68 -

WO 00/23921, provides a substantial description of
library designing.

     After a library is designed the process
proceeds to prepare one or more libraries using
5   material handling apparatuses. FIG. 6 shows an
illustrative flow diagram of combinatorial library
preparation process 600 that controls hardware to
automatically prepare libraries in accordance with the
principles of the present invention. Automated step
10 may be performed manually if desired.

     At step 610, the user may define hardware
resources that are available for use in process 600.
The user may define hardware resources such as
automated liquid handling robots, pump controllers,
15 solid or powder dispensing systems, and other
dispensing equipment. In defining the hardware, the
operating characteristics of such hardware may also be
identified. For example, characteristics such as
configuration of syringes attached to a dispensing
20 device (e.g., in series of parallel), motion limits,
step size and reference positions for arm movements,
dispensing capacity of syringes, etc. may be
identified. Other hardware resources may include
temperature controllers for regulating the temperature
25 or temperature ramp rate of a substrate or pressure of
a reaction vessel.

     At step 620, a recipe file or other
instructions that include the library design is
received by process 600. Step 620 may analyze the data
30 and develop a set of material handling instructions
that can control the hardware to synthesize a library.

- 69 -

The material handling instructions may be provided to, for example, electronic circuitry 112 of FIG. 1 so that control commands can be provided to material handling apparatuses. Then at step 630, the material handling

5 instructions are executed and a library is prepared in accordance with the recipe file received at step 610.

Software that can perform process 600 is described in more detail in WO 00/67086, which is hereby incorporated by reference in its entirety.

10   After salts, crystals, or polymorphs are created in a library format, they are screened for desired properties and characterization. The present invention utilizes high throughput screening that provides sufficient information that enables the

15 process to proceed to the next step. Screening tests are performed to obtain data on each library member. Screening tests can be primary or secondary depending where in the process the test are performed. A minimum number of screening tests may be performed to identify

20 the materials in the library, determine the crystallinity of the materials, and determine the solubility of the materials. Additional tests may be performed to obtain more data on one or more library members.

25   Screening tests may provide quantitative and/or qualitative data. Quantitative data enables the present invention to perform analysis based on numerical data. This data is well suited for use in software programs operating on computers because it can

30 be categorized quickly and accurately. Qualitative data, however, provides information that does not

- 70 -

require intensive number manipulation and relatively
quick material characterization. For example, an
identity screen can run with sufficient precision to
determine if members of the library are different from
5 each other or from a standard. But the identity screen
may not be so thorough that it identifies each member
of the library. In another example, a crystallinity
screen may determine certain crystal characteristics,
such as morphology, without determining every (or even
10 most) characteristics of a crystal (e.g., such as
melting point, unit cell, etc.).

Screening tests may be implemented on
instruments that determine, for example, solubility,
partition coefficient (log P), birefringence (while the
15 sample is wet and/or dry), melting point, crystal
morphology, hygroscopicity, and other physical
characteristics. Other screening test instruments may
provided data using, for example, X-ray diffraction,
Raman spectroscopy, IR or Near IR spectroscopy, UV-Vis
20 spectroscopy, nuclear magnetic resonance spectroscopy
(NMR), gas chromatography and liquid chromatography.
These tests are preferably performed in parallel or in
a rapid serial or automated mode such that the
screening method does not delay the overall process.

25   As illustrated in FIGS. 2A, 2B and 3,
screening test are performed in different steps of the
process. One or more screening test may be performed
at each screening step in a process. Several screening
steps provide greater quantities of data so that
30 library members are more fully characterized than
characterizations performed by a single screening test.

- 71 -

For example, in one embodiment a primary screening step
(e.g., step 225 of FIG. 2A) may perform at least 4
different tests (e.g., solubility, log P, crystallinity
and Raman spectroscopy) to determine which library
5   members should be selected for bulk synthesis. Primary
screening steps preferably use fewer tests than a
secondary screening step so that high throughput
screening can be maximized.

A secondary screening step (e.g., step 255 of
10 FIG. 2B) may also perform several high throughput
screening test to provide the process with a thorough
characterization and identification of the bulk sample.
Secondary screening test may include test such as IR
spectroscopy, Near IR spectroscopy, UV-Vis absorption,
15 X-ray diffraction, melting point, and pK_a. Other tests
that can be performed on bulk samples include NMR,
differential scanning calorimetry, thermogravimetric
analysis and elemental analysis.

A process may perform solubility,
20 birefringence X-ray diffraction, hygroscopicity and/or
Raman spectroscopy in high throughput mode to quickly
and accurately characterize library members. In
particular, when using only solubility, birefringence,
and Raman tests, these tests adequately characterize
25 any salts that may have formed. In addition, these
test also determine whether polymorphs of drug
candidates (or salts thereof) have formed. If desired,
a more detailed identification of the different
polymorphs can then be accomplished through additional
30 screening test and analysis.

- 72 -

Solubility is performed by sampling the
supernatant mother liquor from the recrystallization
step of polymorph generation or from the
crystallization or precipitation step of salt
5   selection, as described above. The liquid sample is
subjected to a concentration detector to determine the
amount of the drug candidate (or salt) in the solvent.
The drug candidate (or salt) concentration may be
detected using liquid chromatography, thin layer
10 chromatography, gas chromatography, absorption in the
UV-Vis range, infrared (IR), fluorescence or any other
suitable technique. In one embodiment, liquid
chromatography coupled with an ultraviolet radiation
detector may be used to determine drug candidate
15 concentration. An example of an liquid chromatography
system is an Agilent 1100LC system.

Sampling for the solubility test is typically
performed at a temperature in which recrystallization
or precipitation has occurred. Solubility testing can
20 be performed as a high throughput screen, which can be
performed in a rapid serial mode or in parallel. The
testing will provide solubility information for the
particular solvent in which the drug candidate salt is
present at which the solution was sampled. In one
25 embodiment, one may determine the solubility of one or
more drug candidates under a variety of conditions in
parallel microtiter plates or other assembly comprising
a plurality of wells by forming arrays of solvents or
solvent mixtures at temperatures ranging from 0° C to
30 70° C and measuring the concentration of the compound
in the supernatant. In a preferred embodiment, the

- 73 -

temperature is measured at a temperature in which the drug candidate or salt is dissolved ($T_{initial}$) and at the final temperature, in which the drug candidate or salt has crystallized (T_{final}).

5   The partition coefficient, also called log P, is a well known measure of solubility in a water/1-octanol mixture. In a high throughput mode, log P is determined by measuring the concentration of the drug candidate salt in both water and 1-octanol at

10 a particular temperature. In a preferred embodiment, the solubility in 1-octanol and the solubility in water is measured in separate wells of a microtiter plate as part of the overal process, with those measurements used to determine log P. In an alternative embodiment,

15 water saturated with 1-octanol and 1-octanol saturated with water may be used as solvents. The concentration may be detected using liquid chromatography, thin layer chromatography, gas chromatography, absorption in the UV-Vis range, infrared, fluorescence, or any other

20 technique that determines concentration known to those of skill in the art. Using any suitable detection device, log P is determined by dividing the concentration in 1-octanol by the concentration in water and taking the log of that number.

25   Birefringence testing may be used to determine the crystallinity of a sample. In particular, birefringence testing indicates the quantity of crystals formed, size of the crystals, and shape of cyrstal (e.g., needle structure, blade

30 structure, tabular structure, or any other structure). FIG. 7 shows several crystal structures that can be

- 74 -

detected using birefringence testing in accordance with
the principles of the present invention. The crystal's
structure may provide information in deciding which
library members are suitable for large scale synthesis.
5 For example, needle crystals are often more difficult
to filter than tabular crystals.

Birefringence testing may be performed by
passing light through wet or dry samples in the
library. Preferably, the samples are arrayed on a
10 transparent substrate located between two parallel and
perpendicularly aligned cross-polarized filters. A
light system may be positioned above or below one of
the filters to detect light refraction as it passes
through samples on the substrate. Persons skilled in
15 the art will appreciate that other devices can be used
to detect birefringence of materials in such a setup.
For example, an array of photo-diodes may by used to
detect birefringence of a material. The light system
advantageously screen the entire substrate in one pass,
20 thus providing a relative fast indication of the
suitability of the materials located on the substrate.
A detailed description of a birefringence testing
device is described in detail in conjunction with
FIG. 28. Also described in conjunction with FIG. 28 is
25 a method for performing light scattering to detect if
any crystalline structures are present.

Because crystals are birefringent structures,
they have the ability to refract light. This property
allows a birefringence testing station to detect if a
30 sample on the substrate is crystalline or amorphous.
Amorphous materials are typically undesirable because

- 75 -

they tend to be unstable and more hygroscopic than crystalline forms. An example of device using a parallel light rotating and collection device is described in U.S. Patent No. 6,157,449 ('449 patent),

5   which is incorporated herein by reference in its entirety. A birefringence testing station may, for example, use the device in the '449 patent in conjunction with a light system.

In situ measurements of an array of material

10 samples can be performed using birefringence or a light scattering technique. More particularly, in situ measurements are performed using a reflective optical scanning technique. A description of an apparatus that performs in-situ monitoring using the reflective

15 scanning technique is described below in specification pertaining to FIG. 30.

One advantage of in-situ measuring is that it maximizes high throughput testing of material samples. For example, assume that an array of material samples

20 are subjected to crystallization conditions while being monitored in situ. Further assume that these particular crystallization condition did not yield any crystalline structures. Instead of disassembling a crystallization assembly and providing the substrate,

25 which does not contain any crystalline structure, to a series of screening test, in situ monitoring can provide information to avoid such an unnecessary step. Performing screening test on material samples that do not contain crystalline structures slows down the

30 screening process for detecting new polymorphs. Thus, in situ monitoring provides information that may result

- 76 -

in subjecting the material samples to different
crystallization conditions that may produce crystals.

Hygroscopicity testing characterizes
materials (e.g., crystals) according to their ability
5   to adsorb water. Hygroscopicity can be tested in an
automated manner using Raman spectroscopy, Near IR
spectroscopy or in situ measurements as a series of
"snapshots" to determine water gain (or loss), as
described in other parts of this specification. PuuMan
10 Oy (Kuopio, Finland) manufactures and markets the HMA
(Hygroscopicity Measurement Apparatus) that is capable
of measuring the hygroscopicity of eight samples
simultaneously.

Hygroscopicity can also be measured by
15 automated weighing systems. For example, vials
containing samples are automatically weighed (for
example using a Bohdan Automated Weighing Station
(called the Balance Automator), available from Bohdan
Automation (a Mettler-Toledo Company, Vernon Hills,
20 IL). The vials containing samples are then exposed to
a controlled atmosphere (e.g., a certain humidity) for
a selected time, after which the vials containing
samples are automatically weighed again, with a
difference in weight being a measure of hygroscopicity.
25 In some embodiments, the automated weighing station can
be located inside a glove box or other atmosphere
controlled chamber.

Hygroscopicity can also be measure using
dielectric measurements. Such dielectric measurements
30 can be performed on a substrate having regions
comprising interdigitized probes, with the samples

- 77 -

being placed in the regions and the substrate being
placed in a controlled atmosphere chamber (e.g., a
controlled humidity chamber). Changes in samples
dielectric properties are measured as water is gained
5 (or lost) and hygroscopicity is determined.

In a preferred embodiment, hygroscopicity is
measured in a high throughput manner using a
microbalance and more particularly using sensitive
mechanical resonators, whose resonance performance can
10 be monitored and correlated with mass. In one
preferred embodiment, hygroscopicity is measured using
a method for screening samples created in accord with
the description herein (e.g., on a universal
substrate), comprising the steps of (a) providing a
15 plurality of solid samples; (b) placing a first sample
onto a mechanical resonator in signaling (e.g.,
electrical, magnetic, optical, thermal, or other
communication) communication with a source of an input
signal; (c) coupling the mechanical resonator with
20 measurement hardware; (d) exposing the samples to a
controlled atmosphere (e.g., moisture or desiccating)
while on the mechanical resonator; (e) applying an
input signal; (f) monitoring a response of the
mechanical resonator to the moisture of the samples
25 thereon with the measurement hardware; and (g)
repeating steps (b) through (f) for each sample for
which measurement is desired. In addition, this method
can readily be adapted for also conducting analysis of
mass change in response to a change of temperature,
30 such as for thermogravimetric analysis.

In this preferred method, the monitoring that

- 78 -

occurs in step (d) may employ a suitable lock-in
amplifier or like hardware for monitoring the change of
frequency of the mechanical resonator while maintaining
the input signal to the resonator as a constant. It may

5   alternatively employ the monitoring of the change in
electrical feedback from the resonator while
maintaining a constant frequency.

In a particularly preferred embodiment, the
input signal is a variable frequency input signal and

10 the monitoring step (d) includes varying the frequency
of a variable frequency input signal over a
predetermined frequency range to obtain a frequency-
dependent resonator response of the mechanical
resonator. The preferred method advantageously allows

15 repeating steps to be performed simultaneously for
analyzing an array of samples in a parallel format.
Yet, as desired the repeating steps may be performed
serially.

When employed in a salt selection or

20 polymorph workflow, as described herein, the preferred
method can be described as comprising the steps of (a)
providing an array of different particulated
pharmaceutical polymorph candidate samples; (b)
providing a tuning fork resonator having at least two

25 tines with tips and being in electrical communication
with a source of an input signal; (c) adhering a
quantity of a plurality of samples to at least one of
the tines; (d) coupling the tuning fork resonator with
measurement hardware; (e) simultaneously, for at least

30 two samples of the array, humidifying the samples while
on the tuning fork resonator; (f) simultaneously, for

- 79 -

at least two samples of the array, applying a variable
frequency input signal; (g) simultaneously, for at
least two samples of the array, varying the frequency
of a variable frequency input signal over a

5   predetermined frequency range to obtain a frequency-
dependent resonator response of the mechanical
resonator to the humidification of the samples; and (h)
graphically displaying the responses for each of the
samples analyzed, such as by providing a readout of a

10   frequency response, wherein frequency versus signal is
plotted.

Another embodiment of the preferred method
contemplates an apparatus for measuring small
quantities of materials, comprising a plurality of

15   resonators, and particularly tuning fork resonators
having tines with tips; a holder for each resonator; a
readout board; a plurality of elongated members for
bridging electrical communication between the resonator
and the readout board; and a frame carrying at least

20   the resonators, holders and elongated members. The
apparatus is preferably adapted for attachment to a
robot arm for facilitating automation of the operation
of the apparatus. The apparatus of may further comprise
other components, such as a sample work surface having

25   a recess therein for receiving a sample, a host
computer, and a power source (e.g., for providing a
variable frequency input signal to the resonators).

The advantages of the preferred method are
numerous, including mass measurements of soft, thick,

30   non-uniform layers or irregularly shaped samples; small
sample quantity measurements (with some samples being

- 80 -

less than about 100 micrograms and more preferably less
than about 50 micrograms); certain resonators (e.g.,
tuning fork resonators) have a Q-factor does not
decrease by more than about 1-3%, so relative change of
5   a sample mass is accurately measured by resonator
frequency change; quick measurements, in some
embodiments in less than one minute (and in other
embodiments in less than about 30 seconds or less than
about 5 seconds for a single sample or for an entire
10   array or library); and the ability for real-time mass
tracking (or real-time hygroscopicity). The details of
this preferred method are set forth in commonly owned,
U.S. Patent Application No. _____, titled "High
Throughput Microbalance and Methods Using Same"
15   (Attorney Docket Number 1012-_____, filed concurrently
herewith), which is incorporated herein by reference
for all purposes. See also U.S. Patents 6,336,353 and
6,182,499, which are both incorporated herein by
reference for all purposes.
20   Raman spectroscopy may be performed using any
type of unit, such as a commercially available unit
(e.g., Renishaw, Ramascope), with an X-Y stage that
addresses the samples in a rapid serial mode. In some
embodiments, in order to run a very high throughput
25   screen, peak assignments may not be performed on the
spectra acquired. Instead, the spectra are used as
"fingerprints" to determine if different polymorphs (or
salts) have formed in the high throughput
experimentation. In other embodiments, peak-matching
30   software may be used to make the determination of
different identity. Raman, IR, X-ray or other

- 81 -

fingerprint type spectra may not be quantitatively
analyzed, and instead may be used for qualitative
determinations about the relative sameness or
differences between spectra. An example of spectra
5   provided in a graph format is illustrated in FIG. 9.

Morphology or crystallinity may also be
performed by inspecting each of the regions of the
libraries under a microscope, for example, with crossed
polarizers. X-ray diffraction can be performed on a
10 Bruker GADDS (Bruker AXS, Madison, WI), See also, U.S.
patent 6,371,640, which discloses a method and
apparatus of screening materials in a high throughput
and library format, incorporated herein by reference.

Thus, selected screening test are used to
15 select drug candidates for further investigation.
Screening test also enable the process to perform
detailed characterization of library members (e.g.,
bulk samples) to determine its suitability. The
recrystallization condition identified based on the
20 selected samples may be used to prepare bulk samples of
the desired salts for additional characterization. One
feature of the process of the present invention is the
use of a "universal substrate". A universal substrate
refers to a substrate having samples thereon and that
25 can be used for a variety of tests (described above)
without manual or other manipulation of the samples.
This will become more apparent in the discussion below.
Thus, a single substrate (e.g., array of materials) can
be tested for birefringence, Raman, X-ray diffraction
30 and melting point without handling the samples for each
test.

- 82 -

Automated control of material screening
device 160 (e.g., birefringence station, Raman station,
XRD station, melting point station, etc.) may
advantageously enhance high throughput screening. High
5   throughput screening is enhanced by automated control
because it allows the process to quickly characterize
drug candidates and provide data to a computer (e.g.,
computer 110 of FIG. 1). Automated control may be
provided by a software program operating on a computer.
10 In particular, software programs may control material
screening device 160 to characterize and identify
properties of drug candidates.

For example, a software program can instruct
material screening device 160 to perform an identity
15 screen of the drug candidates. Because drug candidates
are typically arranged in a library format, the
software can direct device 160 to perform screening in
parallel or in a rapid serial mode. Parallel screening
provides characterization of two or more drug
20 candidates simultaneously. Rapid serial mode screening
provides relatively rapid screening of drug candidates.
on an individual basis.

Data is obtained from material screening
device 160 when it characterizes and identifies
25 properties of drug candidates. This data may be
provided to the software so that analysis can be
performed with respect to each drug candidate. Data
analysis can include categorizing drug candidates,
determining suitable drug candidates (e.g., for salt
30 selection), experimental data categorization, and
determining polymorphs (e.g., for drug candidates,

- 83 -

salts, and other solutions). Data analysis may be
performed one or more times during a process. For
example, data analysis may be performed after an
initial screening to determine which library
5   compositions are suitable for further testing. (This
is illustrated in FIGS. 2A and 3 at steps 230 and 335,
respectively.) If at least one of the library
compositions is suitable for further testing, secondary
data analysis may be performed in the process.
10   Secondary data analysis may yield a substantially more
rigorous examination of data than primary data analysis
and provide accurate results in high throughput.
(Secondary data analysis in a process is illustrated in
FIGS. 2B and 3 at steps 260 and 360, respectively.)
15   Persons skilled in the art will appreciate that data
analysis can be performed as often times as necessary
to characterize and examine data.

FIG. 8 shows an illustrative flow diagram for
determining if a crystalline structure being tested is
20   part of a particular polymorph family or is a newly
discovered polymorph. Categorization flow 800
determines if any material compositions in the library
member should be affiliated with an existing family of
materials (e.g., existing polymorph family) or if it
25   should be placed in a new family of materials (e.g, new
polymorph family). A family comprises a group of
materials (e.g., crystalline structures) that exhibit
similar characteristics. The categorization of various
library members is performed based on data obtained
30   from screening tests (e.g., Raman, XRD, melting point,
solubility, hygroscopicity, etc.). One advantage of

- 84 -

analysis flow 800 is that it can categorize library
members (e.g., hundreds or thousands of materials) into
an appropriate family (i.e., existing or new) without
relying on initial reference data. Initial reference
5 data can also be used, and in some embodiments,
reference data is preferred, such as when a known
polymorph exists and others are being searched.
Categorization flow 800 builds a database of reference
data (e.g,. existing polymorph families) as it
10 categorizes library members with the database being
integrated with known or existing data or not. Based
on this database, categorization flow 800 continuously
analyzes and categorizes crystalline structures created
using, for example, process 200 and/or process 300, as
15 described herein.

In the following discussion of FIG. 8, assume
that there is no prior data for any of the crystalline
structures discussed in this particular example. At
step 810, data obtained from a screening test of
20 crystalline structures of the library array is
provided. Any above-described screening test can be
used to provide data on each crystalline structure. It
is preferred that the data set is an XY dataset. For
example, if Raman, XRD or another spectroscopic
25 screening technique is used, spectra is provided.
Spectra provides data such as peak location, peak
height, and peak width of a crystalline structure. If,
for example, a melting point screening technique is
used, numerical temperature values are provided as data
30 to step 810.

- 85 -

        Assuming that the data obtained at step 810
is the first set of data obtained for the first
crystalline structure, there is no reference data that
can be used for comparison. Thus database at step 820
5   is void of reference data, at least initially. In
particular, step 820 does not have any reference data
that represents a polymorph family. For purposes of
clarity and brevity, any data that is provided from
step 810 that is used in process 800 is referred to as
10 new crystalline structure. Proceeding to step 830, the
data associated with a crystalline structure is
compared to data for each known polymorph family stored
at step 820. Thus, the crystalline structure undergoes
an iterative comparison process, which after each
15 iteration, produces a correlation coefficient. A
correlation coefficient is indicative of how "close"
the crystalline structure is to a particular polymorph
family.

        Persons skilled in the art will appreciate
20 that methods other than iterative techniques can be
implemented to compare the crystalline structure to
each of the existing polymorph families.

        Categorization process 800 may use
statistical methods to obtain the correlation
25 coefficient. Statistical methods may be used to
determine the deviation (e.g., standard deviation) of
the data associated with the crystalline structure to a
reference data set. Software programs that perform
such mathematical functions include MATLAB[®] software
30 sold by The MathWorks, Inc., of Natick, Massachusetts,
Mathemathica[®] sold by Wolfrum Research, Inc. of

- 86 -

Champaign, Illinois, and MathCad° sold by MathSoft of
Cambridge, Massachusetts. Persons skilled in the art
will appreciate that other software programs different
from the programs described above may be used to

5   perform matrix based calculations and other
mathematical calculations.

The comparison process in step 830 uses
different comparison techniques differently based on
the type of data provided by step 810. One such

10 technique is a cross-correlation technique. This
technique is typically used when the measured data is
obtained using Raman spectroscopy. As those of skill
in the art know, Raman spectra it typically a curve or
graph that represents characteristics of a crystal.

15 Such a graph is illustrated in FIG. 9. The cross-
correlation technique performs a point-to-point
correlation to determine how "close" the measured
spectra is to reference spectra. After the comparison
is performed, a correlation coefficient is obtained

20 based on how close the graphs match.

Another technique that can be implemented at
step 820 is a peak matching percentage technique (e.g.,
peak locations are compared). This technique is
typically used comparing spectra obtained by X-ray

25 diffraction (XRD) spectroscopy. In this technique, the
peak locations of an XRD graph are determined using an
algorithm. Then the determined peak locations are
compared to peak locations of reference data (e.g.,
peaks of particular polymorph family). A percentage

30 value is obtained based on how similar the XRD peaks

- 87 -

are to the reference peaks. This percentage value is
analogous to the correlation coefficient.

        After the iterative comparisons are
performed, the best correlation coefficient is obtained
5   at step 840. The best correlation coefficient is
associated with the polymorph family that the new
crystalline structure set matched best.

        At step 850, the best correlation coefficient
is compared to a predetermined value. Typically, the
10   predetermined value is a user-defined correlation
coefficient that sets the threshold for determining
whether the data associated with the crystalline
structure should be associated with an existing
polymorph family.

15   If the correlation coefficient exceeds the
predetermined value, that crystalline structure is
grouped into the polymorph family associated with that
best correlation coefficient at step 860. After
step 860, process 800 returns to step 810, which
20   provides the next new crystalline structure to step
830.

        If the correlation coefficient does not
exceed the predetermined value, a new crystalline
polymorph family is created based on the data obtained
25   on the new crystalline structure at step 870. In the
event that there was no reference polymorph family for
any comparison to be performed, the crystalline
structure is automatically used to create a new
polymorph family at step 870. The data associated with
30   the new polymorph family is provided to step 820 for
use as a reference as an existing polymorph family.

- 88 -

Also, after step 870, process 800 returns to step 810.
Data from a whole series of libraries based on a single
drug candidate can be sorted in continuous process so
that one set of families are created that are
5   indicative of the individual forms of the drug
candidate.

        Thus, analysis process 800 illustrates
crystal structure categorization based on screened
data. Persons skilled in the art will appreciate that
10 steps shown in FIG. 8 are merely exemplary and that
additional steps may be added and some steps may be
omitted or modified.

        If desired, reference data such as a computer
file, a look up table, or other suitable information
15 source may be provided to the database in step 820.
Parameters that were used to create the library members
can be provided to database in step 820. For example,
parameters such as solvents added to the salt,
crystallization temperature, and other parameter used
20 to formulate library arrays and crystallize the arrays.
This data can be used as criteria in grouping
crystalline structures.

        Storing measured data provides a database
that stores data (e.g., spectra) from each library
25 member. This advantageously enables currently measured
data to be compared to other previously screened
libraries. In some embodiments, when a new family of
polymorphs is discovered in step 825, data from
previously identified families may be compared to newly
30 acquired data. This enables analysis process 800 to
determine if the "new" family corresponds to a

previously identified family such that the data can be assigned to an existing family. This effectively reduces the total number of families of data and allows for a high correlation within a family or group of

5 data. Yet, user defined variation between families or groups is still preserved. In other embodiments, if original data is not provided, the first experimentally determined data can be used as the "starting" information (e.g., step 820 can use data from a

10 designated well or a designated piece of information).

An illustrative example of pre-formulation system 100 (FIG. 1) that implements process 800 to categorize different library members is described in conjunction with FIGS. 9-12. In the following example,

15 assume that each library member of a 96 well substrate has been tested using a device (e.g., an infra-red device, UV-Vis absorption device, a Raman device, an X-ray device) that obtains data. Using such devices, the data can be arranged in a graphical format. FIG. 9

20 illustrates spectral data obtained from four different library members using a Raman device. The spectral data shows that each of the library members contain polymorphs of the same drug candidate, but are similar enough to be classified as part of the same family or

25 group.

FIG. 10 illustrates spectral data obtained from three different library members using, for example, an X-ray diffraction device. FIG. 10 shows that these three library members also have polymorphs,

30 but are each different from each other such that they are not part of the same family group.

- 90 -

FIG. 11 shows an illustrative interactive
display screen 1100 that includes several spectral
graphs of screened library members. Display
screen 1100 shows that spectra 1105 are arranged in
5 array format 1108. Preferably, spectra 1105 are
arranged so that they coincide with the layout of the
substrate in which they were screened. As shown in
FIG. 11, not every portion of array 1108 has spectral
element. This may be because a crystal did not form
10 during the crystallization (e.g., recrystallization)
process.

FIG. 11 also shows that a user can enter and
change spectrum sorting parameters 1110. For example,
a user can enter a minimum grouping correlation
15 coefficient. As described above in conjunction with
FIG. 8, the correlation coefficient may be used to
determine if a crystalline structure belongs to a
particular family. The value entered for the
correlation coefficient can range between -1 and 1.
20 The closer the correlation coefficient is to 1, the
more stringent the criteria becomes for placing a
particular library element in an existing family. For
example, if there are ten library elements and the
correlation coefficient is .9, each library element may
25 be associated with a new family -- thus creating ten
different families. If the correlation coefficient is
closer to zero, then matching a particular library
element to an existing family becomes less stringent,
thereby producing fewer new families. The value
30 selected for a correlation coefficient typically ranges
from about 0.5 to about 0.9. The correlation

- 91 -

coefficient selected may, for example, be the
predetermined value used at step 850 in process 800.

A user can select whether to use a fixed
reference (e.g., a predetermined reference) or an
5   arbitrary reference (e.g., a library element) for
providing a baseline in determining family grouping
selection. Persons skilled in the art will appreciate
that additional parameters may be entered or modified
as suitable within the spirit of the invention. A user
10 may also change the image size of array 1108 by
changing width and height parameters 1115. Users can
submit their entries by selecting send overlay 1120 or
they can reset their entries by selecting reset
overlay 1122.
15   In another embodiment, categorization process
800 may be implemented with an XY dataset where
similarity among xy data sets is measured by a
correlation coefficient (CC) ranging from -1.0 to +1.0,
with +1.0 being a perfect match to be in the same
20 group, which is used for data deemed of insufficient
quality. The sorter has a default group, namely the
junk group. The parameters for determining the data to
be junk or not can be set by the user, with each data
set being checked to see if it is junk before being
25 placed in this default location. When a data set is
not put into the default location, a new group may be
created by comparing the xy data set from the remaining
data to a reference and for each unclassified sample xy
data set using the reference set from each existing
30 group (or one can pull out all sets from each existing
group). Comparison of the sample data to the reference

- 92 -

set can provide a CC value (or comparison of the sample
data to the sets and get a best CC value from the
comparisons). This is followed by retention of the
best CC and the Group where the CC comparison came

5   from. If the best CC is less than the specified value,
then the sample is put in the new group; otherwise the
sample is put into the group from which the best CC was
obtained. The user can override the automated
classification by performing comparisons visually and

10   assigning groups manually. This can also be
implemented on peak locations, peak heights or other
data. Thus, for XRD data, it is currently preferred
that peak locations are used to determine a correlation
coefficient.

15   In another embodiment, the process also
allows the user to define a recycle bin, where data can
be designated for re-running through the correlation
process. In this manner, the user can identify data
that should be sorted based on different parameters.

20   In still another embodiment, the user can iterate the
correlation process, by running multiple correlations
based on at least one different parameter.

             FIG. 11A shows one example of a dialog
box 1150 for the user to define the parameters used in

25   correlating the spectra. One side of the box 1150
allows the user to define the automatic junk
classification 1152, which as described above allows
for removal of data from the classification workflow.
The do it check 1154 enables or disables this feature,

30   with the settings that the user can define included in
the remainder of the box 1152. The moving average

- 93 -

point 1156 is used for smoothing the signal of the
data. The minimum peak height 1158 is used for setting
the height that a peak in the xy data set must meet in
order to be considered to be a peak for correlation
5 purposes (e.g., this feature can set background noise
levels and allow the correlation process to ignore the
noise). The minimum zero crossings 1160 allows the
user to set the minimum number of zero crossings for
peaks, with the implicit assumption that each peak has
10 two zero crossings as a default. The maximum zero
crossings 1162 allows the user to set the maximum
number of zero crossings in a data set so that the data
would be considered to have good quality. For example,
spectra with too many zero crossings may signify that
15 the spectra may simply comprise noise.

          The match algorithm 1164 side of box 1150 is
used for setting the correlation factors. The coverage
1166 has settings for single and all, with single
comparing the sample to a master or reference data of
20 the existing family or form only. The resulting score
represents the comparison score between the sample and
the reference data for a particular family. The all
setting compares the sample data to all of the data
already in the family, in which case that best
25 correlation score represents the best score resulting
from all the comparisons. The method 1168 allows the
user to decide on what part of the data will be used
for correlation. As shown in FIG. 11A, peak center
performs correlation based on the peak locations
30 (within an acceptable deviation as defined in the peak
center band width 1172). Other methods of correlation

- 94 -

include full signal correlation, which uses the entire
data set for correlation. Differential signal method
of correlation performs correlations based on the
digital difference signals (first derivative) of the

5 sample and reference data. Baseline removed method of
correlation performs correlation based on data with the
curvatures and slopes removed in the data. Other
methods of correlation are within the skill of one of
skill in the art, including for example with spectra,

10 peak height or peak width. The typical correlation
coefficient 1170 is the setting to determine the
allowable difference to obtain the best correlation
coefficient. The peak center band width 1172 allows
for the user to set an allowable deviation in peak

15 centers in spectra data sets. The minimum peak height
1174 generally performs the same function as 1158, and
moving points average 1176 allows the user to average
set number of data points together for correlation
purposes.

20   FIG. 11B shows an example of a dialog
box 1180 that allows the user to set the parameters for
performing the correlation. The user sets the minimum
correlation coefficient, as discussed above, with
box 1182. The user can allow for previous sorting

25 results to be used in a new sort by either checking or
un-checking box 1184, with use of previous sort results
allowing for re-cycling the data, as discussed above.
The region of interest 1186 portion allows the user to
define a certain portion of the data to consider in the

30 correlation workflow, for example if only a certain
region of a spectra would be of interest, then this

- 95 -

portion can be used for correlation. As shown in
box 1180, this particular embodiment allows the user to
set-up to five interval ranges 1190 (with a lower
setting (low X) and an upper setting (high X)).

5   FIG. 11C shows dialog box 1192 that allows
the user to manually move data from one group (e.g.,
family or form) to another group (or family). This
feature allows the user to manually create families
used for correlation or to manually change

10   correlations.

          When the user selects send overlay 1120
(FIG. 11), the process may analyze the spectral data in
accordance with the parameters defined by the user.
For example, the process may utilize the principles

15   illustrated in FIG. 8 to analyze and group each library
element to an existing or a new family. FIG. 12 shows
an illustrative display screen 1200 that has organized
each of the library elements of FIG. 12 according to
their respective family. In particular, display

20   screen 1200 shows that library elements are grouped
into twelve different families. Thus, each of the
library elements are grouped accordingly.

          A user may repeatedly change the correlation
coefficient and select send overlay 1120 to generate

25   different groupings of library members in spectra 1105.
For example, if user desires to generate six families
of library elements, the user may change the
correlation coefficient achieve such a result. A user
may desire to do this because a particular number of

30   families is known or expected. The user may know how
many families are expected because a different test

- 96 -

(e.g., a Raman, hygroscopicity, XRD, melting point)
previously yielded such a result.

One advantage of using the software described
herein is that a user can run several categorization
5   tests based on different data sets. For example, a
user can categorize library members based on data
obtained from, solubility, log P, crystallinity,
melting point, hygroscopicity, crystal morphology and
birefringence, as well as X-RAY diffraction, infrared
10 (IR), Near IR, and Raman spectroscopy, among other
screening techniques. After categorization is
performed based on two or more such tests, the results
of each categorization can be cross-referenced to
determine inconsistencies and/or to validate findings
15 of potential new polymorphs.

As described above in conjunction with
FIGS. 2A, 2B, and 3, processes 200 and 300 prepare and
screen, and analyze library members to group different
polymorphs. Because it is an object of the present
20 invention to provide high throughput testing of
polymorphs, software can be implemented to optimize the
screening process. Software can minimize the number of
screening test that need to be performed for a
particular library member. Thus, increasing the
25 capacity of the number of library elements that can be
tested for polymorphs.

FIG. 12A shows an illustrative flow diagram
of a software process 1270 that determines which
library members should be subjected to further testing
30 in accordance with the principles of the present
invention. Process 1270 begins at step 1272 in which

THIS PAGE BLANK (USPTO)

- 97 -

each of the library members are subjected to an initial
screening. Screening, as described above, provides
data to a computer, and based on that data,
process 1270 can determine whether a particular member
5   is suitable for additional testing. Preferably, the
initial screening is a relatively fast screening such
as birefringence testing.

At step 1274, process 1270 determines whether
the data associated with a particular library element
10   meets certain criteria. The criteria, which is
provided by step 1275, includes data that provides a
basis or threshold value for selecting which library
member should be selected to performed additional
testing. For example, if birefringence testing is
15   used, the criteria may be whether any type of crystal
structure is present in the library member. The
criteria that can be selected for setting the threshold
can be selected by a user or the computer program
making the determination.

20   In one embodiment, later screening tests
(such as Raman, XRD, etc.) can be performed only on
samples having a birefringence image with an arithmetic
mean above a determined point. The arithmetic mean may
be in this case the mean of all the pixel intensities
25   from an image of the library member under birefringence
conditions.

If the data shows that a crystal structure is
present in the library member, then that member is
suitable for additional testing at step 1276. If,
30   however, the data indicates that no crystal structure
is present in that library member, that member is

- 98 -

marked as not suitable for additional testing at
step 1278. Once a library member is selected, more
screening tests (e.g., Raman, XRD, melting point) may
be performed. Because performing additional tests take
5   time, process 1270 efficiently eliminates unnecessary
testing, thereby maximizing the throughput of the
overall process (e.g., workflow).

If desired, the selective screening process
can be progressive. That is, assume that a particular
10   library element was selected in an initial screening
and was subjected to a second screening (e.g., an XRD
screening). Applying the principles described in
process 1270, the same library member does not have to
be subjected to additional screening test if it fails
15   to meet a minimum criteria standard based on the second
screening.

The following describes several apparatuses
that are used to implement processes for selecting
salts and discovering polymorphs. In addition, the
20   following discussion describes how such apparatuses are
used in conjunction with the processes illustrated in
FIGS. 2A, 2B, and 3.

Processing of the selected drug candidate or
salt(s) for discovery and characterization of suitable
25   forms requires at least two, but preferably three
steps, to be carried out in a combinatorial or high
throughput mode. The two required steps are
dissolution of the drug candidate or salt(s) thereof,
and crystallization of the candidate from solution.
30   The optional third step that can occur between the
dissolution and crystallization steps is separation of

- 99 -

any remaining solids from the solution by filtration or
centrifugation. This optional step may be necessary to
eliminate nucleation sites for the crystallization
step.

5   A general reactor assembly is shown in
FIG. 13. A reactor assembly is used for formulating
drug candidates, solvents, acids, bases, etc. Reactor
assemblies can be used to dissolve solutions for salt
selection or to dissolve solutions for polymorph
10   testing. Reactor assemblies such as reactor assembly
1300 of FIG. 13 are suitable for containing reactions
of interest.

            FIG. 13, for example, illustrates a cross-
sectional view of reactor assembly 1300 that can be
15   used for preparing library members in accordance with
the principles of the present invention. As
illustrated in FIG. 13, reactor assembly 1300 is
constructed in microtiter format. Reactor
assembly 1300 includes reactor block 1302 that is
20   constructed with one or more wells 1304. Each reactor
block 1302 can receive reaction vessels 1306.
Materials such as drug candidates and solvents are
mixed in reaction vessels 1306. Reaction vessels 1306
are isolated from one another to prevent cross-
25   contamination among the reaction vessels. This can be
accomplished by securing sealing sheet 1308 over
reaction vessels 1306 by fastening cover plate 1310 to
reactor block 1302 with fastening device 1312 (e.g., a
bolt, screw, clamp, etc).

30   Persons skilled in the art will appreciate
that any suitable number of wells 1304 may be

- 100 -

constructed. For example, a reactor assembly may have
96 wells or it may have 384 wells.

Reactor block 1302 and cover plate 1310 may
be constructed of any suitable material such as metals
5 (e.g., steel, aluminum), plastics, and ceramics.
Materials such as aluminum or an aluminum alloy may be
preferred because they have desirable thermal and
structural properties. Reaction vessels 1306 may be
plastic or glass, with glass being preferred. Sealing
10 sheet 1308 is typically made from a material that is
chemically resistant to the reaction of interest taking
place in reaction vessels 1306 as well as being elastic
for its sealing properties. Sealing sheet 1308 may be
constructed from materials such as Teflon®, silicone
15 rubber, Vitron®, Kalrez®, or equivalents. If desired,
sealing sheet 1308 may be constructed with two or more
such materials.

Materials can be dispensed into reaction
vessels 1306 by hand or by automated robots. Automated
20 equipment may increase the speed and accuracy of
step 212 (FIG. 2A). Liquid handling robots such as
those sold by Cavro Scientific Instruments, Inc. of
Sunnyvale, California may be used for automatically
dispensing materials. The description associated with
25 FIG. 6 explains in more detail how the present
invention can control robots to dispense materials into
reaction vessels 1306.

FIG. 13 provides a general example of one
such reactor assembly that can be used in the present
30 invention. FIG. 15 illustrates a more detailed reactor
assembly that can be used for formulating a library.

- 101 -

FIG. 15 is discussed below in the apparatus section of
the detailed description. Also described in the
Apparatus section are other assemblies and tools that
facilitate preparation of materials. For example,
5   FIGS. 24-28 illustrate heating devices that heat
materials contained within the reactor vessels.

Heating and/or agitation of the reaction
mixtures in each vessels is often used to promote
dissolution of the candidate material in the solvent.
10 Prior to dissolution, mixing/stirring balls or magnetic
stirrers (e.g., fleas) may be added to the reactor by
hand or with a device such as that shown in FIG. 14 (as
discussed in detail below). The reactor block may then
be placed on a rocking, rotating, or vortexing plate
15 that is fixed with a heating element for mixing and
heating reaction contents. The magnetic stirring
apparatus described above may also be used to agitate
the materials. Also, the heating element may be
programmable to provide a desired heat cycle.

20 Adding a glass or metal ball to each vial can
improve agitation during the dissolution/synthesis
step. FIG. 14 and FIG. 14A illustrate a three-
dimensional view and an exploded three-dimensional
view, respectively, of object dispensing assembly 1402,
25 which dispenses several objects in parallel in
accordance with the principles of the present
invention. Dispensing assembly 1402 can be secured
over a reactor assembly such as reactor assembly 1300
using flaps 1409 that extend from sidewalls 1408 to
30 line up with the outer edges of reactor block 1302
(shown in FIG. 13).

RECTIFIED SHEET (RULE 91)

- 102 -

Dispensing assembly 1402 has a cover 1404
that covers a cavity 1406 formed by sidewalls 1408 and
bottom plate 1411. Bottom plate 1411 is preferably
constructed with a plurality of holes that align to
5   receptacles (e.g., wells or vials) in batch
reactor 1300 when dispensing assembly is attached to
batch reactor 1300. Also included in dispensing
assembly is a separation assembly 1410. Separation
assembly 1410 includes isolation plate 1412 and sliding
10 plate 1414. Isolation plate 1412 may have an array of
guide holes that guides an object (e.g., ball or
magnetic stirrers) to the holes of sliding plate 1414.
The operation of dispensing assembly 1402 will be more
apparent in the following paragraph.
15   An excess of objects (e.g., balls) is held in
cavity 1406. From this excess of objects, a single
object is placed in each guide hole of isolation
plate 1412 by shaking assembly 1402. A single object
is transferred into each hole of sliding plate 1414 by
20 moving sliding plate 1414 to a first position that
aligns the holes in it with the guide holes in
isolation plate 1412. In this first position, the
holes in sliding plate 1414 do not align with the holes
in bottom plate 1411. The objects cannot be dispensed
25 directly into the receptacles in the reactor base
below, therefore, one ball is retained in each hole of
sliding plate 1414. Only one ball is retained in
sliding plate 1414 because it is constructed with a
thickness that substantially equal to the thickness
30 (e.g., diameter of ball) of the object. Sliding
plate 1414 is then moved to a second position which

- 103 -

aligns the holes therein with the wells or vials in the
reactor base below (via the holes in bottom plate
1411), and simultaneously moves these same holes out of
alignment with the guide holes in isolation plate 1412.
5   This permits the object contained within each hole in
bottom sliding plate 1414 to drop into the
corresponding receptacle below. It should be noted
that dispensing assembly 1402 can be modified to
dispense different diameter balls by changing
10 separation assembly 1410. The parallel dispensing
device shown in FIG. 14 may be used for dispensing
other small solids such as stirring fleas.

Regardless of whether agitation objects
(e.g., balls) are added to the reactor assembly, an
15 array of solvents or solvent mixtures is added to vials
contained within the reactor assembly. The contents
are sealed in their respective vials and then agitated
at a specified temperature for a predetermined period
of time. The temperature typically ranges from about
20 20°C to about 10°C lower than the boiling point of the
most volatile solvent in the array. The time period
typically ranges from about one hour to about 24 hours.
In addition, the mixture may be accelerated by
mechanical agitation. In a preferred arrangement the
25 solution is mixed through the use of a vortexer,
sonicator, shaker, incubator, or other suitable shaking
and heating devices.

Once the solution is fully mixed, the
supernatant liquid may be isolated from any residual
30 solid either by hot filtration or by centrifugation.
The concentration of the solid dissolved in the

- 104 -

supernatant liquid can then be measured by using any
suitable technique such as liquid chromatography, gas
chromatography, thin layer chromatography, infrared or
Raman spectroscopy, and UV-Vis adsorption (as discussed
5 below).

After the materials are mixed, the cover of
the reactor assembly is removed and aliquots of the
solution (typically a supernatant or mother liquor) are
removed and transferred to a glass substrate or a
10 universal substrate and allowed to cool. Glass
substrates such as borosilicate reactor plates sold by
Zinsser Analytic GmbH of Frankfurt, Germany, may be
used in the process. As the solution cools, crystals
may form. The rate in which the substrate is cooled
15 can be controlled. For example, the substrate may be
subjected to a chilled bath, a thermal module, or a
chilling incubator which is sold by Torrey Pines
Scientific, Inc., Solana Beach, California.
Alternatively, particularly when volatile solvents are
20 used, evaporation techniques may be used to generate
crystals. If desired, precipitation and slurry
techniques can also be used.

After cooling, evaporating, precipitating, or
slurry, the supernatant may be removed in a suitable
25 manner (e.g., by aspirating with a pipette and/or
wicking away the solvent with filter paper).
Supernatant removal can be performed either manually or
automatically using a computer controlled device.
Supernatant removal can also be performed in serial
30 (e.g., rapid serial mode) or in parallel (e.g., a
twelve tip pipette can be used for parallel pipetting).

The supernatant and the crystals can both be analyzed
for their composition, identity, and properties.

The above description described how a reactor
assembly and substrate are used for performing the
5   processes of the present invention. The following
embodiment describes various assemblies that
advantageously provide generation of and high
throughput screening of salts and polymorphs.
FIGS. 15, 16 and 21 illustrate three different
10 assemblies that have several components in common.
Although three assemblies are shown, those of skill in
the art will recognize that the functions of these
assemblies may be combined into two assemblies or into
one assembly. Three assemblies are used herein to
15 provide a process that can be implemented relatively
quickly using each assembly. When the assemblies of
FIGS. 15, 16, and 21 are coupled for use with automatic
robots, the process may be performed more quickly and
accurately.

20   FIG. 15 illustrates reaction assembly 1500
which is in accordance with the principles of the
present invention. Reaction assembly 1500 is used for
a dissolution process, which can include, for example,
mixing an array of solvents to a drug candidate and
25 heating the mixture to prepare hot saturated solutions.
In addition, dissolution processes can include mixing
acidic or basic reactants to a drug candidate to form
salts. Moreover, the mixture of chemicals added to
formulation assembly 1500 may based on a library model.
30   Reaction assembly 1500 is generally similar
to batch reactor 1300 in FIG. 13, but is different in

several respects. Reaction assembly 1500 includes a
bottom plate 1510 that has a shock-absorbent layer 1512
positioned on top. Shock-absorbent layer 1512 may
include a foam pad or other elastic material.

5   Positioned above these parts is reactor base 1514,
which is constructed with an array of holes that can
receive vials 1516. Reactor base 1514 and shock-
absorbent layer 1512 are secured to bottom plate 1510
using bolts 1511. A barrier sheet 1518 and a septum

10 sheet 1520 are positioned over vials 1516. Barrier
sheet 1518 is designed to seal the top openings of
vials 1516 and to prevent solvents from mixing with
other vials. Barrier sheet 1518 may be made of Teflon®
or other suitable material. Both barrier sheet 1518

15 and septum sheet 1520 may be pierced by a needle or
cannula. Reactor cover 1522 is placed over septum
sheet 1520 and has holes 1523 therethrough to allow a
needle or cannula to pass through. Reactor cover 1522
is secured to reactor base 1514 with bolts 1521.

20   Although bolts 1511 are specifically
discussed herein, other means such as clips, clamps or
vices for securing parts of reaction assembly 1500 can
be used. FIG. 15 also shows a registration pin 1515
that allows parts (e.g., reactor base 1514, barrier

25 sheet 1518, etc.) to be aligned when being secured
together. Several registration pins 1515 may be used
to provide accurate alignment.

            Vials 1516 pass through the holes of the
reactor base 1514 so that the bottom of vials 1516 rest

30 on shock-absorbent layer 1512. Typically vials 1516
are closed at the bottom (i.e., like a test tube with a

- 107 -

rounded or flat bottom). Shock-absorbent layer 1512 is
made of a resilient material (such as foam) that
provides resistance to vertical displacement when
downward pressure is applied to vials 1516. Thus,
5   assembly 1500 isolates each vial when the reactor parts
are secured together and provides tolerance for
dimensional differences among vials 1516. FIG. 15
shows 96 vials in an eight by twelve array, but those
of skill in the art will recognize that a different
10 number or arrangement of vials may be used in any
particular experiment or format.

If desired, ball dispensing assembly 1402
(shown in FIG. 14) may be used to dispense balls into
each vial 1516 prior to sealing reactor cover 1522.

15   FIG. 16 illustrates a partially exploded view
of filtration assembly 1600 which is in accordance with
the principles of the present invention. After the
mixture is prepared in reaction assembly 1500, aliquots
from each vial may be placed in filtration
20 assembly 1600. Filtration assembly 1600 separates
particles (e.g., supernatant) of the aliquot, thereby
providing a "seedless" solution of the aliquot that can
be tested. In addition, filtration assembly 1600
facilitates preparation of an array of parent
25 solutions, which may be daughtered for additional
testing.

Liquids are taken from individual wells from
the reaction assembly 1500 using a manual or automated
pipetting instrument (as described herein) and
30 transferred to the corresponding vials in the array of
wells in filtration assembly 1600. The bottom portion

- 108 -

of filtration assembly 1600 includes bottom plate 1610,
fasteners 1611, shock-absorbent layer 1612, reactor
base 1614, and vials 1616. These parts (1610-1616) may
be the same parts (1510-1516) as that of the reaction

5   assembly 1500. This allows for common parts to be
prepared and used in different assemblies, which
reduces manufacturing costs.

    Filtration assembly 1600 differs from
reaction assembly 1500 by the addition of filter

10 subassembly 1630 and top plate 1624. In addition,
filtration assembly 1600 contains a sealing layer 1617
that is similar to barrier sheet 1618 except that
sealing layer 1617 has pre-formed holes for allowing
the filtered solution to enter vials 1616. These holes

15 have a slightly smaller diameters than vials 1616, thus
when filter subassembly 1630 is secured to base 1614
such that sealing layer 1617 provides a seal between
vials 1616.

    Filter subassembly 1630 in FIG. 16 has two

20 primary functions. Filter assembly 1630 facilitates
filtering of the samples received from reaction
assembly 1500, and it allows sampling of the filtrate
from vials 1616. These functions can be accomplished
by combining filter subassembly 1630 with a top plate

25 1624. Top plate 1624 provides at least two positions
for a cannula or needle to deliver or aspirate
solutions to vials 1616 in filtration assembly 1600.
This arrangement allows for fluid communication between
vials 1616 and the top of filter assembly 1600.

30 Specifically, top plate 1624 has holes 1625A and 1625B
that correspond to some of or all of vials 1616 in

- 109 -

reactor base 1614. For example, hole 1625A may be used
to introduce fluid and hole 1625B may be used to
withdraw fluid from vials 1616. Details of the
apparatus for introducing solutions to be filtered into
5   vials 1616 or withdrawing filtered solution from vials
1616 are discussed below.

Filter subassembly 1630 is shown in detail in
FIG. 17. Filter subassembly 1630 includes a bottom
mid-layer 1632 to support filter layer 1634. Filter
10 layer 1634 is used to separate nucleation sites or
other undissolved materials from the solution so that a
substantially pure solution is provided to vials 1616
(shown in FIG. 16). Filter layer 1634 may be populated
with an integrated filter and gasket 1635. Sealing
15 plate 1636 is fitted over filter layer 1634 and
provides support for top mid-layer 1638. Bottom
mid-layer 1632 has receiver hole 1633A and adjacent
hole 1633B located over the upper opening of some or
all of the vials or wells in reactor base 1614
20 (FIG. 16).

Holes 1633A and 1633B permit introduction and
withdrawal, respectively, of a solution to vials 1616
(FIG. 16). Sealing plate 1636 supports a large o-ring
1740 and small o-ring 1744 for each region or vial.
25 When filter subassembly 1630 is assembled, each large
o-ring 1740 forms a seal between sealing plate 1636 and
top mid-layer 1638. This seal, formed by large o-ring
1740, prevents vapor crosstalk between vials 1616.
Another seal is formed when a needle passes through
30 small o-ring 1744. Persons skilled in the art will
appreciate that other materials may be used to provide

- 110 -

seals. For example, seals may be formed with valves
such as a Merlin valve sold by Merlin Instrument Co. of
Halfmoon Bay, California.

FIG. 18 illustrates o-ring sheets 1850 that
5   may be positioned on sealing plate 1636 (FIG. 16) in
accordance with the principles of the present
invention. Large o-ring 1851 and small o-ring 1852 can
be manufactured in sheets for easier positioning on
sealing plate 1636. As illustrated, o-ring sheet 1850
10 is constructed in a four-by-four array of o-rings.
Thus, if a reactor base has 96 wells, then six o-ring
sheets 1850 would be required to fully populate a 96
well assembly. Other sizes of o-ring arrays may be
used based on the size of each o-ring array and the
15 overall number of regions or vials in the reactor
assembly. For example, the o-rings may be arranged in
an 6x8 array, an 8x8 array, or any other suitable
combination.

FIG. 19 shows a close-up isometric view of a
20 portion of FIG. 17. In particular, FIG. 19 shows first
channel 1920 and second channel 1930 that are formed
when filter subassembly 1630 is assembled. First
channel 1920 may correspond to hole 1633A, which may be
used for introducing liquid into the filtration
25 assembly. In addition, FIG. 19 shows filter 1634
positioned between bottom mid-layer 1632 and sealing
plate 1636. Thus, when liquid is deposited into first
channel 1920 via hole 1633A, it is filtered before
being deposited in the receptacle. Second channel 1930
30 may correspond to hole 1633B, which provides a path in

- 111 -

which a needle or cannula can directly withdraw
filtrate.

In an alternative embodiment, filters may be
cut to size so that individual filters are placed into
5   bottom mid-layer 1632, instead of single sheet of
filter paper. Filter paper may be cut to size by knife
edge ring 1921 that are part of bottom mid-layer 1632.
Knife edge ring 1921 may, for example, be associated
with the first channel. When a user places filter
10   paper on bottom mid-layer 1632 and impresses it onto
each knife edge ring 1921 (only one shown), an array of
filter disks on mid-layer 1632 is provided.

FIGS. 20A and 20B illustrate how pipette
system 2060 dispenses into and/or retrieves materials
15   out of vials 1616 using filtration assembly 1600. In
particular, FIG. 20A shows a cross-sectional view of
filtration assembly 1600 and pipette system 2060 that
has needle 2020 extending through hole 1625A. Passing
needle 2020 through hole 1625A enables the process to
20   utilize filtration assembly 1600. FIG. 20B illustrates
an enlarged view of filtration assembly 1600 encircled
with dashed line "6B" in FIG. 20A. Here, needle 2020
is inserted into hole 1625A such that it pierces
barrier sheet 1618, septum sheet 1620, and protrudes
25   through small o-ring 1744. As described above, when
needle 2020 and small o-ring 1744 interact, a seal is
formed. This seal enables solvent to be dispensed into
hollow channel 2060 without risk of contaminating other
vials. Solvent is dispensed into hollow channel 2060
30   and is passed through filter layer 1634 or,
alternatively, through a filter disk (not shown) to

- 112 -

receiver 2061. Receiver 2061 is located in bottom
middle layer 1632 and is typically made of chemically
resistant material (e.g., plastic) that is designed to
prevent wicking away of the solvent passing through
5   filter layer 1634.

The seal between the needle 2020 and small
o-ring 1744 should be capable of withstanding
sufficient pressure to allow the liquid to be injected
into the channel 2060. Bottom mid-layer 1632, sealing
10 plate 1636, and top mid-layer 1638 are typically made
of metal (such as stainless steel or aluminum). The
filter material in filter layer 1634 or filter disk can
be made of an appropriate filtering material that is
stable with respect to the solvent media, including
15 materials such as glass microfiber filter pads,
cellulose, Teflon[*], paper, and other materials used for
sample filtration with organic solvents. Filter layer
1634 can comprise a single sheet of filtering material
so long as the process is run to avoid cross talk
20 between different array members. Alternatively,
several pre-cut filters may be positioned above
channel 2061.

FIG. 20C illustrates how pipette 2060 can
either dispense or retrieve solvent directly from
25 vial 1616. For example, needle 2020 can extend
through hole 1625B, barrier sheet 1618, septum
sheet 1620, and filter assembly 1630 to directly access
vial 1616. This advantageously provides fluid
communication between needle 2020 and vial 1616 without
30 using filtering sheets of filtering assembly 1600.

- 113 -

Pipette system 2060 can dispense or retrieve
liquids at a specified temperature to prevent undesired
crystal formation or precipitation. Pipette
system 2060 may utilize, for example, heat sink 2042
5 and a cartridge heater (not shown) (e.g., a FIREROD
heater) to maintain a specified temperature. A
cartridge heater may be housed in cavity 2043.
Extending from the needle 520 is a wire (not shown)
that is wound around heat sink 2040. Because the wire
10 is coupled to heat sink 2040, heat generated in heat
sink 2040 is conducted to needle 2020. Thus,
needle 2020 is maintained at a temperature that
prevents aspirated liquid from cooling. Other designs
may be employed to maintain the liquid at the desired
15 temperature, such as a heated tip on a needle, as shown
in U.S. Patent No. 6,260,407, which is incorporated
herein by reference in its entirety.

FIG. 21 illustrates crystallization
assembly 2100 that is designed to permit the formation
20 of crystals in accordance with the principles of the
present invention. Mixtures may be obtained from
vials 1616 of filtration assembly 1600 and dispensed in
crystallization assembly 2100. Alternatively, mixtures
may obtained from vials 1516 of reaction assembly 1500
25 (shown in FIG. 15). Crystal formation may occur, for
example, by cooling the mixture, evaporating the
mixture, by precipitating the mixture, or by slurrying
the mixture.

One benefit of having separate filtering and
30 crystallization assemblies is that the array of
filtrates taken from filtration assembly 1600 can be

- 114 -

placed into two or more crystallization
assemblies 2100, allowing for crystallization under
different conditions or methodologies. For example,
this methodology allows for a temperature study to be
5   performed in which more than one array of solutions is
crystallized, each at a different temperature. As
mentioned earlier, using interchangeable parts in the
different assemblies allows for efficiency in inventory
and parts uniformity. The different assemblies also
10   permit flexibility in process flow for each part of the
recrystallization procedure.

Crystallization assembly 2100 has lower
reactor base 2160. Reactor base 2160 has recessed
region 2161 that is constructed to receive
15   substrate 2164, which is resting on top of pad 2162.
Pad 2162 should be selected to help avoid breaking the
substrate. This pad is preferably foam, silicone
rubber, or another resilient material.

Substrate 2164 provides a suitable surface
20   for crystal formation. Moreover, substrate 2164 can be
transferred to the desired analytical equipment to
enable characterization of the array of crystals. The
substrate may be constructed from an optically
transparent material, such as glass, to allow for
25   direct optical studies of the crystals on the
substrate. It can also be made of other materials such
as plastic. Substrate 2164 may have a substantially
flat surface on which the crystals are contained.
Substrate 2164 may have distinct regions on its surface
30   to support crystals formation. For example, those
distinct regions may be round, square, etc. The

- 115 -

regions may also be recessed to readily retain
crystals. Thus, dimples or wells can be used. (A
dimple herein is defined as a depression with a rounded
concave surface, and a well is a recess with one or
5   more defined sidewalls.)

Above substrate 2164 is gasket 2166 having an
array of holes (not shown) that correspond to the array
of regions on substrate 2164. When assembled, these
lower components (pad 2162, substrate 2164, and gasket
10   2166) will fit into recessed region 2161 so that
gasket 2166 is secured substantially flush against the
upper outside edges of reactor base 2160.
Crystallization reactor 2168 is placed over these
components and secured to reactor base 2160 using bolts
15   2170 or other securing means (clips, clamps, nuts,
etc.). The securing means should provide sufficient
force to compress gasket 2166, which in turn seals the
regions on substrate 2164 from potential crosstalk.

Crystallization assembly 2100 also includes
20   sheet 2172 (typically made of Teflon®) and septum 2174
(which may be identical to barrier sheet 2118 and
septum 2120, respectively) and reactor cover 2176
covering crystallization reactor 2168. Reactor cover
2176 is similar to reactor cover 2122 for reaction
25   assembly 1500, having holes through which needle 2020
may pass. The parts over crystallization reactor 2168
are secured to crystallization reactor 2168 by bolts
2178 (although other clamping, clipping or securing
means may be used). Thus there are two sets of secured
30   components in crystallization assembly 2100. The first
set includes crystallization reactor 2168, gasket 2166,

- 116 -

substrate 2164, pad 2162, and reactor base 2160. The
second set includes sheet 2172, septum 2174, and
reactor cover 2176, which together are coupled to
crystallization reactor 2168. These separate sets
5 permit the bottom part of crystallization assembly 2100
to be assembled without the upper portion, resulting in
more flexibility in being able to use part or all of
crystallization assembly 2100 for pre-formulation
testing.

10   Reactor cover 2176 and septum 2174 may not be
used if evaporation studies are to be tested with the
material samples contained within cyrstallization
assembly.

         FIG. 21A illustrates an alternative
15 embodiment of a crystallization assembly 2102 that is
designed to permit formation of crystals in accordance
with the principles of the present invention.
Crystallization assembly 2102 includes similar parts as
crystallization assembly 2100 such as reactor
20 base 2160, substrate 2164, and reactor 2168. Not
included with crystallization assembly 2102 is pad 2162
and gasket 2166. Instead substrate 2164 is positioned
directly on top of reactor base 2160 and o-rings 2104
are added to crystallization assembly 2104. O-
25 rings 2104 may be comprised of a sheet of o-rings (as
shown in FIG. 21B) or it they can be a two-dimensional
arrays (e.g., 4x4 array of individual o-rings). When
crystallization assembly 2102 is assembled, o-
rings 2104 are pressed flush against substrate 2164 and
30 reactor 2168 to provide effective isolation of material

- 117 -

samples deposited into the crystallization assembly 2102.

FIG. 21C is a partial cross-sectional view of crystallization assembly 2102 that illustrates how the through-holes of reactor 2168 and respective portions

5 of substrate 2164 are isolated from each other by o-rings 2104. Also shown in FIG. 21C are the wells 2106 in which o-rings 2104 reside. Thus when substrate 2164 is pressed against reactor 2168, o-rings 2106 are pressed against substrate 2164 and wells 2106, thereby

10 providing a substantially airtight seal that isolates each region of the substrate.

When aspirating from or dispensing material into a sealed vial through a septum using a needle or similar device, the accuracy in controlling the volume

15 of material transferred can be affected by the changing volume and pressure within the vial. One solution to this problem has been to use a coaxial needle, which consists of two tubes attached together along their axises. One tube is used to transfer material to or

20 from the vial, and the second tube is used as a vent to equilibrate pressure between the vial interior and the surroundings.

The coaxial needle device presents several shortcomings. Because the two-tube assembly is much

25 larger than a single needle, it will create larger holes when piercing a septum that may not seal properly when the needle is removed. Also, because the tips of the tubes remain at a fixed distance with respect to one another, the range of depths in the vial to which

30 material can be introduced or withdrawn is limited. Dispensing a large amount of material into a deeper

- 118 -

vial, for example, may lead to material flowing out of
the vent tube if the tip of the vent tube becomes
submerged. These shortcomings of the prior art are
addressed by the venting needle device described in
5 conjunction with FIGS. 22A and 22B.

FIG. 22A shows a venting needle assembly 2200
that can be used to aspirate from, or dispense
materials into, sealed vials or receptacles. Venting
needle assembly 2200 comprises venting needle 2202,
10 liquid handling needle 2204, body 2206, guide
rods 2208, springs 2210, and guide block 2212.
Body 2206 is attached to a liquid handling system (not
shown) that controls aspiration and dispensation of
liquid through liquid handling needle 2204. Liquid
15 handling needle 2204 extends a fixed distance from body
2206 and passes through movable guide block 2212.
Venting needle 2202 also passes through movable guide
block 2212, essentially parallel to liquid handling
needle 2204, and extends a fixed distance from the
20 lower face of guide block 2212. Guide block 2212 is
attached to guide rods 2208, and configured so that it
can slide along the central axis of liquid handling
needle 2204. Guide rods 2208 are configured to slide
into body 2206 when force is applied to the lower face
25 of guide block 2212. Springs 2210 are located on guide
rods 2208, between body 2206 and guide block 2212.
These springs return guide block 2212 to a fully-
extended position, determined by the length of guide
rods 2208, when there is no force on the lower face of
30 guide block 2212.

- 119 -

As described above, reactor assembly 1500,
filtration assembly 1600, and crystallization assembly
2100 each include a sealing layer (e.g., septum) for
isolating each vial or receptacle from each other. For
5   purposes of brevity and clarity, venting needle
assembly 2200 is described in conjunction with reactor
assembly 1500. Venting needle assembly 2200 is not
limited to being used only with reactor assembly 1500,
but it can be used with any suitable assembly
10 comprising sealed vials or receptacles. If desired,
venting needle assembly 2200 can be used in place of
pipette system 2060.

After reactor assembly 1500 is sealed, each
vial contains a fixed volume of material. Venting
15 assembly 2200 prevents the pressure from changing when
aspirating liquid from or dispensing liquid into a
sealed vial, which permits increased accuracy in
controlling the volume of material transferred.
Venting assembly 2200 accomplishes this by using a dual
20 needle assembly, wherein one needle is used to
aspirate/dispense and the other is used to vent the
vial.

In a typical material transfer process,
venting assembly 2200 is lowered over reactor assembly
25 1500, either manually or by mechanical means, until the
lower surface of guide block 2212 contacts the upper
surface of reactor cover 1522. Both venting
needle 2202 and liquid handling needle 2204 extend far
enough from guide block 2212 to extend through holes
30 1523 above the vial of interest, and pierce septum
sheet 1520 and barrier sheet 1518 (if present). When

- 120 -

venting needle 2202 pierces septum sheet 1520 (and
barrier sheet 1518, if present), it provides an open
passageway between the upper portion of the vial and
the surrounding atmosphere, which maintains equilibrium
5   between the pressure in the vial and the ambient
pressure (i.e., pressure outside the sealed vial).
Thus, when liquid is aspirated from or dispensed into
the vial by liquid handling needle 2204, the pressure
does not change because venting needle 2202 provides
10 the substantially constant pressure with the vial.

Body 2206 may be pushed towards the top of
reactor assembly 1500 until liquid handling
needle 2204, which is attached to body 2206, reaches
the desired depth within the vial for dispensing or
15 aspirating a liquid. Body 2206 may contain a mechanism
(not shown) the heat liquid handling needle 2204 to a
predetermined temperature. As liquid handling
needle 2204 extends into the vial, guide rods 2208
slide further into body 2206 and as springs 2210
20 compress, as shown in FIG. 22B. During this procedure,
venting needle 2202 extends a fixed depth into the
sealed vial, preferably with the tip of venting
needle 2202 located near the top of the vial, above any
liquid which may be present. This device thus permits
25 transfer of a liquid to and from vials having different
depths while maintaining a venting passage that
equilibrates pressure between the interior of the vial
and the ambient atmosphere. When the transfer of
liquid is complete, body 2206 may be pulled away from
30 reactor assembly 1500, causing liquid handling
needle 2204 to withdraw from the vial and springs 2210

- 121 -

to expand until guide block 2212 reaches its fully-
extended position, as shown in FIG. 22A. Pulling body
2206 further away from reactor assembly 1500 removes
both venting needle 2202 and liquid handling

5   needle 2204 from reactor assembly 1500 through holes
1523. The device may then be inserted into another
hole over a different vial and the above procedure
repeated.

Temperature is an important parameter in the

10 various formulations, filtration, and crystallization
operations that enable salt selection and polymorph
production. For example, in some methodologies it is
desirable to heat reaction assembly 1500 to dissolve as
much drug candidate as possible in the solvent(s). In

15 processes where temperature is important (e.g., during
crystallization), any of assemblies 1300, 1500, 1600 or
2100 (shown in FIGS. 13, 15, 16, and 21, respectively)
may be placed in an oven, cooler, or other temperature-
controlled chamber (such as the Torrey Pines incubator

20 cited herein).

It may be desirable in some processes to have
precise control of temperature. One method for
controlling the temperature of the assemblies during
certain stages of the workflow is shown in FIG. 23,

25 which depicts three-axis robot 2300, having arms 2305
and 2310 and plurality of pumps 2334, situated by work
surface 2330. Pumps 2334 are in fluid communication
with a solvent or other liquid and in fluid
communication with needles 2320 and 2322. Heated block

30 assembly 2350 is positioned on work surface 2330.
Heated block assembly 2350 is configured to contain

- 122 -

reaction assemblies 1500, filtration assemblies 1600
and those assemblies to assist mixing material samples.
It may be desirable to heat filtration assembly 1600 to
prevent crystallization during the filtering process.

5   Not shown in FIG. 23 is a magnetic stirring device that
can tumble magnetic stirring fleas to agitate materials
contained within the assemblies. Also located on work
surface 2330 are several temperature-controlled
housings 2500. Temperature-controlled housing 2500 is

10   described in more detail in conjunction with the
description accompanying FIG. 25. Housing 2500 can
contain an assembly such as the reactor assembly 1300,
reaction assembly 1500, filtration assembly 1600, or
crystallization assembly 2100. FIG. 23 also shows deck

15   assemblies 2370 that hold various assemblies for use in
a workflow.

         Detailed structure of the temperature-
controlled housing is not critical to this invention,
and may simply comprise insulated walls with a

20   resistive heater regulated by a thermocouple for
temperature control. These types of heaters are sold
commercially as the FIREROD™ heaters available from
Watlow of St. Louis, Missouri.

         FIG. 24 illustrates an exploded view of

25   temperature-controlled housing 2350 shown in FIG. 23.
Temperature-controlled housing 2350 includes tub 2410
and tub support fixtures 2430 and 2440. Tub 2410 is
constructed from a material (e.g., aluminum) having
desired thermal conductive properties. As shown,

30   tub 2410 has pockets 2412 and 2414 for containing an
assembly (e.g., reactor assembly 1500 or filtration

- 123 -

assembly 1600). Tub 2410 has fluid channels (not
shown) in which a fluid or gas is provided to heat or
cool the tub. Fluid inlet/outlet ports 2354 provide
connections to allow a desired heating or cooling fluid
5   or gas to flow through the channels, thereby heating or
cooling an assembly placed in housing 2350. The
temperature-controlled housing shown in FIG. 24 may be
surrounded by an insulating layer to improve thermal
control and stability.

10   Another embodiment that facilitates
temperature control of a reactor or assembly is shown
in FIG. 25. FIG. 25 illustrates thermal control
chamber 2500 having top 2570 and bottom 2580 that mate
to form an enclosure. Top 2570 has cavity 2572 therein
15   and bottom 2580 has cavity 2582 therein, which together
define the enclosure. Cavity 2572 is preferably sized
to accommodate at least one of the assemblies 1300,
1500, 1600, or 2100 (shown in FIGS. 13, 15, 16, and 21,
respectively).

20   In a preferred embodiment, top 2570 has
holes 2574 to allow for communication through top 2570,
(e.g., by a needle, cannula or pipette), for aspirating
or dispensing liquids into the regions, vials or wells
of the assembly in the cavity when top 2570 and
25   bottom 2580 are closed together. A fluid that heats or
cools the thermal control chamber may flow through top
2570 and/or bottom 2580. The fluid flow preferably
maintains a specific temperature substantially
throughout the assembly contained therein. A
30   temperature variation of about 2°C across the enclosed
assembly is generally acceptable, but a temperature

- 124 -

variation of less than about 1°C is desirable.

Top 2570 and bottom 2580 are made of a material (e.g., aluminum) with good heat transfer properties. Suitable fluids with well-characterized thermophysical

5 properties (e.g., water, glycol, etc.) flow through top 2570 and/or bottom 2580 for heating or cooling.

Thermal control chamber 2500 can apply a thermal profile to the assembly contained therein. The thermal profile may, for example, subject the assembly

10 to a range of temperatures that vary with time or to a temperature that is substantially the same for the chosen time period throughout the thermal control chamber. For example, the temperature of the thermal control chamber may ramp up to a predetermined

15 temperature a specified rate, stay at the predetermined temperature for fixed period of time, and then ramp down to ambient temperature after a specified period of time.

FIG. 25 shows thermal control chamber 2500

20 wherein top 2570 and bottom 2580 are connected by hinge 2586 that allows the top and bottom to pivot with respect to each other. This configuration allows for easier alignment and fastening of the top and bottom of the thermal control chamber that contains an assembly

25 such as crystallization assembly 2100 (shown in FIG. 21). When top 2570 is pivoted about hinge 2586, it aligns with bottom 2580 so that cavities 2572 and 2582 meet to enclose the assembly within the chamber.

A typical fluid flow path can occur as

30 follows. Thermal fluid enters either top 2570 or bottom 2580 first and then flows through the inlet,

- 125 -

transverse, and outlet conduits. Then fluid passes
through external conduit 2588 and into the other half
of the chamber where the flow pattern is repeated.
Thus, if the thermal fluid enters top 2570 first, it
5 will flow through the top, exit the top and be
channeled into bottom 2580, flow through the bottom,
and then exit the bottom. The flow direction may also
be reversed if desired, so the thermal fluid enters the
bottom before the top. Rotating fluid transfer hinge
10 2587 may be provided on either side of hinge 2586 which
allows top 2570 and bottom 2580 to pivot with respect
to each other without adjusting external conduits 2588.
This function could also be accomplished with flexible
external conduits and a loop, however, the arrangement
15 shown in FIG. 25 is a preferred embodiment as it avoids
the need for flexible tubing.

     Although not shown in FIG. 25, chamber 2500
has a window that provides a means for a device to
monitor the arrays of material samples contained within
20 chamber 2590. A glass sheet is coupled to this window
with a gasket. Preferably a purge of dry gas (e.g.,
nitrogen) is provided to prevent condensation from
developing when chamber 2590 cools. This ensures that
the monitoring equipment has an unobstructed access to
25 the material samples. For example, in-situ measuring
requires an unobstructed access to monitor the
materials samples that are subjected to crystallization
conditions.

     The structure that facilitates fluid flow is
30 shown in more detail in FIG. 26, which depicts a
cutaway view of the channels that define the fluid path

- 126 -

in top 2570 and/or bottom 2580 of thermal control
chamber 2500. The heating/cooling fluid enters via
fluid inlet 2590, which leads to inlet conduit 2592. A
plurality of transverse conduits 2594 lead from inlet
5   conduit 2592 to outlet conduit 2598 and to fluid outlet
2599. Inlet conduit 2592 and outlet conduit 2598 are
preferably larger in diameter than the transverse
conduits 2594 so that the fluid entering inlet 2590
will flow uniformly through all of transverse
10 conduits 2594. This flow pattern for the
heating/cooling fluid assists in uniform heating or
cooling of control chamber 2500

        Transverse conduits 2594 pass on either side
of holes 2574, if present. Larger conduits 2592 and
15 2598 may be formed by drilling holes through a block
and then plugging one end of each with a large plug
2595 for ease of manufacture. Smaller transverse
conduits 2594 can be formed in a similar manner, with
both ends of the drilled holes capped off by small
20 plugs 2596.

        In operation, a thermal fluid such as water,
glycol, or glycerol is transported from a uniform
temperature reservoir (not shown) to top 2570 or
bottom 2580 of thermal control chamber 2500 through a
25 fluid line using a constant or variable-speed pump.
The thermal fluid enters inlet conduit 2592 through
inlet port 2590. The thermal fluid flows through
transverse conduits 2594 and into outlet conduit 2598.
The thermal fluid then exits through fluid outlet 2599,
30 where it then returns to the reservoir or is routed
through another top or bottom.

- 127 -

A heat pump or other device may be used to regulate the temperature of the thermal fluid in the reservoir by adding or removing heat through a heat transfer coil located in the reservoir. In one
5 embodiment, a processor receives signals from temperature sensors located in the reservoir, and adjusts the amount of heat added to or removed from the thermal fluid through the coil. One or more temperature sensors (not shown) may also be mounted in
10 the top or bottom of the thermal control chamber and connected to the processor. Temperature control can then be achieved by varying both the temperature of the thermal fluid in the reservoir and the flow rate through the conduits. To adjust the flow rate of
15 thermal fluid through the fluid flow system, the processor communicates with a valve located in a reservoir outlet line. Various parts of the system can also be insulated to improve temperature control and stability.

20   FIG. 27 shows a cross-sectional view of thermal control chamber 2500 with crystallization assembly 2100 enclosed therein. This view shows insulation 2591 can be packaged with thermal control chamber. Cross-sectional view 2700 illustrates

25 additional details of the components just described above in conjunction with FIGS. 21, 22, 25, and 26.

Determining the melting point of salts and drug candidates is an important characterization technique for the screening process. In particular,

30 differences in melting point among crystals or amorphous precipitates of a given compound comprise one

- 128 -

of the best indicators for determining the existence of polymorphs.

In one embodiment of the present invention, a melting point station is employed to determine the

5 melting point of the solid material contained in each region of an array following salt formation, precipitation, crystallization, or other similar procedure in the process. Melting points of various materials may be determined by controllably raising the

10 temperature of the substrate containing the array while monitoring the birefringence image (if present) of one or more regions of the array. The temperature at which the birefringence image from a region of the array disappears indicates a transition from the solid to the

15 liquid state. This transition state corresponds to the melting point of the solid matter (generally crystals or amorphous solid) in that region.

Generally, this measurement is based on melting point measurements known in other fields of

20 endeavor. See, e.g., Magill, J.H. "A new method for following rapid rates of crystallization. II. Isotactic Polypropylene." *Polymer* 1962, 3, 35-42; Ding, Z. and Spruiell, J. E. "An experimental-method for studying nonisothermal crystallization of polymers at high

25 cooling rates", *J. of App. Polymer Science Part B - Polymer Physics*, 1996, 34, 2783-2804; Garetz, B. A., et al., "Birefringence and diffraction of light in ordered block-copolymer materials" *Macromolecules*, 1993, 26, 3151-3155; Carlson, E. D. et al. "Mechanical

30 and Thermal Properties of Elastomeric Polypropylene" *Macromolecules*, (1998), 31(16), 5343-5351; and Carlson,

- 129 -

Eric David, "A rheo-optical investigation of the
relaxation and crystallization behavior of stereoblock
polypropylene synthesized from 2-arylindene metallocene
catalysts," Stanford Ph.D. Dissertation (1998); each of
5   which is incorporated by reference.

A melting point apparatus designed to
determine melting points of an array of solids on a
substrate is shown in FIG. 28. Melting point
apparatus 2800 determines the melting points of an
10   array of samples by monitoring the optical properties
of the samples for phase transitions. Melting point
apparatus 2800 can also measure recrystallization
kinetics during thermal cycling. Melting point
apparatus 2800 can use a light scattering or
15   birefringence measuring technique to determine when a
sample transitions from a crystalline structure to an
amorphous liquid. When performing birefringence
measuring, a transmissive or a reflective technique can
be used.

20   Apparatus 2800 detects the melting point of
material samples as follows. First, a sample array is
prepared via crystallization. Those of skill in the
art will appreciate that a sample array can be prepared
by other methods other than crystallization. For
25   example, an evaporation or a precipitation method can
be used. It will also be appreciated that solid
materials (e.g., may be prepared by hand or
automatically by a robot. The sample array may be
contained on a glass slide (e.g., universal substrate)
30   or other transparent material that is placed into a
carrier block. If desired, the carrier block can be

- 130 -

covered to contain any moisture that forms from
products of material decomposition such as
condensation, solvent vapors, etc. Finally, the
carrier block is placed into a temperature chamber such
5   as thermal control chamber 2500 or is placed within two
insulated plates (FIGS. 28A and 28B), which form a
quasi-isothermal block.

        After the material samples are placed in the
temperature chamber, an individual light source and a
10   detector are aligned to each material sample in the
array. Operating in transmission mode, each light
source transmits a light signal through a material
sample. The light source can any suitable device such
as, for example, light emitting diodes, lasers, or
15   incandescent lights. Collimated, polarized, intense,
monochromatic light is preferable for operation, but
weak light (e.g., incandescent light) can also be used.
The light signal can comprise a wavelength ranging
between about 300-2000 nanometers (nm). If desired, a
20   single light source can be distributed to each material
sample by, for example, a fiber-optic bundle, a
telecentric lens, a telescope, collimating optics, or
other similar apparatus. Alternatively, a single light
source or an array of light sources may be moved across
25   each material sample to illuminate a single material or
a row of such materials at a time. Persons skilled in
the art will appreciate that any suitable arrangement
of light sources can be used to provided light-
scattering or birefringence testing.

30   If a reflective technique is used, the light
path does not pass through the material samples.

- 131 -

Rather, the reflection of light off a crystalline
structure is detected. This technique is described in
detail in conjunction with in-situ measuring assembly
3000 of FIG. 30. The reflective technique operates
5   generally as follows. Light emitted from a light
source passes through a first polarizer, then it
reaches a beam splitter that redirects the light
towards a material sample. If desired, the light can
be "pre-polarized" (e.g., a laser) so that a first
10   polarizer is not needed. Light reflected from the
material sample passes back to the beam splitter, but
passed through the beam splitter. If the light signal
has been altered (e.g., polarized) by the material
sample, then it may pass through a second polarizer
15   that is rotated 90° from the first polarizer and
detected by a detector.

Light provided by the light source first
passes through a polarizing filter, then through the
material sample, through a second polarizing filter
20   that is oriented at 90° with respect to the first
polarizing filter. If the material sample does not
contain a crystalline structure, then the light signal
will be extinguished by the second polarizing filter,
thereby preventing a detector from detecting the light
25   signal. If the material sample contains a crystalline
structure, however, the crystal will rotate the
polarization of the light, thereby allowing some of the
light to pass through the second polarization filter.
Any light that passes through the second polarization
30   filter is detected by the light detector.

- 132 -

Various detection methods can be used to
detect light emitted by the light source(s).
Individual detectors such as photodetectors (e.g.,
silicon photodiode, photovoltaic cell, etc.) may be
5　positioned with respect to each material sample. Each
photodetector is connected to a computer (e.g.,
computer 110) that monitors the output of each
detector. Based on the output signals of the
photodetectors, the computer can determine at what
10　temperature a crystalline structure melts. Likewise,
if a detector such as a camera, a charge-coupled device
(CCD) a digital camera, or a video camera is used to
detect phase transitions, aa computer may register the
transitions and calculate the melting point
15　temperature.

Initially, before the chamber begins to heat
the material samples, each detector can ascertain
whether a crystal structure is present. Because each
detector is connected to a computer or other data
20　logging device, each detector can constantly monitor
each material sample. This is useful because when the
material samples are heated, they eventually melt, and
the detectors detect this phase transition. When the
crystal melts, it becomes amorphous, and light is no
25　longer able to pass through the second polarizing
filter. When a detector no longer detects a previously
existing light signal, it is at this temperature that
the crystal has melted.

The temperature of the material samples are
30　ramped up at user defined rate to a user defined
maximum temperature. The rate of temperature increase

- 133 -

is precisely controlled and uniform throughout the
material samples. This enables apparatus 2800 to
accurately measure melting point temperatures.
Alternatively, the temperature can be step up in
5   controlled increments. Furthermore, the temperature of
each material sample can be controlled individually.

        The above discussion was primarily directed
to birefringence testing, but the present invention is
not limited to such. Different birefringence testing
10 can be performed. For example, the polarization angle
of one or both polarization plates can be modulated.
The frequency of the light can be modulated. In
another approach, the above mentioned light scattering
approach can be implemented by removing the polarizer
15 plates. Light scattering, for example, is another
testing method that can be implemented to detect
crystalline structures contained in the sample array.

        Apparatus 2800 includes two main assemblies:
thermal platform 2810 that can support and controllably
20 heat and cool an array (i.e., a substrate containing
samples), and opto-mechanical platform 2830 that
permits simultaneous optical imaging of some or all of
the regions on the array.

        Thermal platform 2810 includes thermal
25 platform top 2812 and thermal platform base 2814, which
when assembled together create cavity 2816 that
supports a substrate or suitable testing platform
(e.g., a carrier plate). Thermal platform 2810 is made
of any suitable material that has high thermal
30 conductivity such as aluminum, aluminum alloys, or
copper. Other materials such as indium, lead, tin, or

- 134 -

silver may be used to form part or all of thermal
platform 2810 to enhance conductivity and improve
temperature uniformity. The substrate may be
constructed from borosilicate glass, or is a Zinnser™

5   plate, or is made of some other optically transparent
or translucent material. The substrate is preferably
positioned to provide optimal thermal conduction with
thermal platform 2810. For example, substrate 2164
(FIG. 21) can be placed in thermal platform 2810.

10   Thermal platform 2810 is shown in detail in
FIGS. 28A and 28B. FIG. 28A shows an isometric view of
melting point apparatus 2800 (computer not shown) that
shows thermal platform 2810 and light source
array 2832. As described above, thermal platform 2810

15   includes thermal platform top 2812 and thermal
platform bottom 2814, which are also shown in FIG. 28A.
Thermal platform 2810 is shown to be in an OPEN
position. That is, pneumatic press 2860 is in a
position such that thermal platform top 2812 and

20   thermal platform bottom 2814 are not pressed against
each other. Pneumatic press 2860 is used to assist
opening and closing thermal platform 2810.

             FIG. 28B shows a cross-sectional view of the
FIG. 28A taken along line 28-28. Thermal platform 2810

25   is also shown to be in the OPEN position. One skilled
in the art will appreciate that when thermal
platform 2810 is closed, thermal platform top 2812 and
thermal platform bottom 2814 are pressed flush against
one another to fully enclose substrate 2864 contained

30   therein. Preferably, a glass cover sheet is placed

.- 135 -

over substrate 2864 to contain any products of
composition (e.g., condensation, out-gassing).

Both thermal platform top 2812 and thermal
platform bottom 2814 have through holes 2823 in which
5 resistive heating elements can be contained. Theses
resistive heating elements, which are described in more
detail below, provide a mechanism for heating
substrate 2864 at a controlled rate while maintaining a
uniform temperature distribution.

10   Referring back to FIG. 28, thermal platform
base 2814 is designed to be heated by elements attached
to or embedded within thermal platform base 2814. In a
preferred embodiment, thermal platform base 2814
contains channels (not shown) that are similar to
15 conduits 2592, 2594, and 2598 in FIG. 26. A thermal
fluid from a reservoir (not shown) can flow through
these channels to heat the substrate in a controlled
manner, as described above. A thermal fluid at a lower
temperature can also flow through these channels or an
20 adjacent set of such channels to cool thermal platform
base 2814.

Alternatively, one or more resistive heating
elements 2822 may be attached to or embedded in thermal
platform base 2814 to provide a mechanism for heating
25 thermal platform base 2814. Resistive heating
elements 2822 may include, for example, wire-wound
resistive heaters, thermoelectric devices (e.g.,
peltier junctions) and thin- or thick-film resistor
heaters. Resistive heating elements 2822 may be
30 embedded or attached to thermal platform base 2814 to
permit improved control of thermal uniformity or

- 136 -

specific temperature profiles in thermal platform 2810.
Different resistive heating elements 2822 may be
capable of distributing different quantities of heat
(i.e., the power consumption may vary). Various
5   resistive heating elements 2822 that have different
power consumption may be placed strategically on
thermal platform top 2812 and thermal platform
base 2814 to promote uniform temperature distribution.
A combination of channels for heating/cooling by flow
10   of thermal fluid and resistive heating elements 2822
may also be used. Those skilled in the art will
recognize that other methods of heating or cooling
thermal platform base 2814 in a controlled manner may
also be used.

15   Another method for heating or cooling the
material samples is to subject the samples to a gaseous
bath such as that provided by a convection oven. Yet
another method is to heat each material sample
individually, or in a serial fashion with individual
20   heaters.

Thermal platform 2810 may also have one or
more embedded or attached thermal sensors 2820 that can
be used in connection with appropriate external
equipment (e.g., datalogger, computer, etc.) to monitor
25   the temperature of the platform. These sensors may be
in the top or bottom of platform 2810, and may include
one or more of the following: thermocouples, resistance
temperature detectors (RTD's), or semiconductor-based
thermistors. One or more of these sensors may be
30   located either in the top, in the bottom, or in both
the top and bottom of thermal platform 2810. Signals

- 137 -

obtained from these sensors are preferably connected to
a computer (e.g., computer 110 of FIG. 1) to permit
automated monitoring and control of the temperature.
The sensor signals can be processed using appropriate
5   control software to regulate current in resistive
heater elements, if present, or to regulate the
temperature and flow rates of thermal fluids in
channels, if present, or to provide more accurate
control of both heating and cooling rates in thermal
10   platform 2810.

Various sensor arrangements can be used to
accurately determine the melting point of crystalline
structures. The temperature of each material sample
may be individually measured, interpolated from an
15   array of neighboring sensor, or extrapolated from a
single sensor. Sensors may be located on thermal
platform 2810 or some other heat transfer medium (e.g.,
convection oven). Sensors may be located directly on
the sample substrate such as directly below a well
20   containing a material sample.

Thermal platform 2810 implements a heating
system that is capable of raising the temperature of
thermal 2810 platform and an enclosed substrate from
ambient temperatures to a user defined temperature. at
25   a user defined rate. For example, the user can select
the maximum temperature to be about 200°C, 280°C,
300°C, or any other suitable temperature. The rate at
which the temperature can be increased or decreased can
also be set by the user. For example, a user may set
30   the rate of temperature deviation at about 0.5°C per
minute, 1.0°C per minute, 2.0°C per minute, or some

- 138 -

other suitable temperature variation. Persons skilled
in the art will appreciate that thermal platform 2810
may heat or cool an enclosed substrate to any suitable
temperature. In addition, thermal platform 2810 may
5 heat or cool an enclosed substrate at any rate.
Moreover, thermal platform 2810 may cycle the
temperature to perform re-crystallization studies.

Thermal platform top 2812 is constructed with
an array of upper optical holes 2813 that corresponds
10 to an array of lower optical holes 2815 of thermal
platform base 2814. Holes 2813 and 2815 are similar to
holes 2574 in thermal control chamber 2560 shown in
FIG. 25, are located above and below some or all of the
regions on a substrate when the substrate is placed in
15 thermal platform 2810. Holes 2813 and 2815 are
associated with a region of a substrate are constructed
to provide an optical pathway that passes through
thermal platform 2810. This optical path is preferably
in a direction substantially perpendicular to the
20 enclosed substrate, and intersects at least a portion
of the region of the substrate associated with the
upper and lower holes.

Opto-mechanical platform 2830 in FIG. 28
includes light source array 2832 and sensor array 2834
25 arranged on opposite sides of thermal platform 2810.
Opto-mechanical platform 2830 may be similar to that
taught in U.S. Patent 6,157,449, which is incorporated
herein by reference in its entirety. Light source
array 2832 may includes one or more laser diodes, light
30 emitting diodes (LEDs), or other controlled light
sources 2833. Alternatively this array may comprise

- 139 -

one or more light sources that are segregated by
mirrors or prisms to form an array of beams. Sensor
array 2834 includes a group of sensors 2835 such as
photo diodes, charge-coupled devices (CCDs) or other

5   optical sensors, which are preferably positioned on the
side of thermal platform 2810 that is opposite light
source array 2832. First polarizing sheet 2840,
typically a commercially-available polarizing filter or
polarizing mirror, is mounted between the light source

10 array and the thermal platform. Second polarizing
sheet 2842 is mounted between thermal platform 2810 and
sensor array 2834 at a cross-polarizing orientation of
approximately 90° with respect to first polarizing
sheet 2840.

15   If desired, the orientation of second
polarizing sheet 2842 may not be positioned exactly at
90° with respect to first polarizing sheet 2840.
Rather, second polarizing sheet 2842 may be positioned
a few degrees (e.g., 1-5 degrees) above or below a

20 perfect 90° cross-polarization. This slight deviation
from perfect cross-polarization prevents extinction of
unaltered light signals provided by a light source.
But this deviation still allows for detecting changes
in crystals using a birefringence monitoring technique

25 and/or a light scattering monitoring technique.
        Light source array 2832, light sensor array
2834, polarizing sheets 2840 and 2842, and thermal
platform 2810 are configured so that optical path 2850
exists between one or more of the light sources and

30 opposing light sensors that passes through polarizing
sheet 2840, thermal platform 2810 including a region on

- 140 -

the substrate mounted therein, and second polarizing
sheet 2842. The orientation of second polarizing sheet
2842 filters or blocks nearly all of the light that
originates from light source array 2832 and traverses
5 optical path 2850 without passing through any
materials. Thus, if light passing through a material
and has its polarization changed, it may pass through
second polarizing sheet 2842 and be received by light
sensor array 2834. If this occurs, then the
10 birefringence image of the material (e.g., crystal) may
be obtained.

     The melting point apparatus described above
permits detection of phase transitions, including the
solid-to-liquid transformation, that may occur on
15 individual wells or regions of a substrate. A
substrate containing deposits of candidate salts,
neutrals, solid precipitates, or filtrates to be
characterized may be located on one or more regions of
the substrate. This substrate may be placed into
20 thermal platform 2812, which in turn is placed into
opto-mechanical platform 2830 to perform optical
scanning. Thermal platform 2810 is configured so upper
and lower optical holes 2813 and 2815 align with
optical paths 2850. This operation may be performed
25 manually or automatically using robot arms to provide
for a more fully automated procedure which reduces the
possibility of errors in handling the samples.

          The temperature of the thermal platform
containing the substrate and one or more material
30 samples is then increased at a defined rate and
monitored. In a preferred embodiment, one or more

- 141 -

temperature sensors in contact with the substrate are
used to provide real-time temperature data to an
external data collection and processing device such as
computer (e.g., computer 110 of FIG. 1). The computer
5   may also be interfaced to the heating/cooling system
described above to provide feedback for better
temperature control. In a typical process, the
temperature of the thermal platform is raised from
ambient temperatures to about 200°C, or from ambient
10   temperatures to about 300°C, at a rate of about 0.5°C
per minute, 1.0°C per minute, 2.0°C per minute, or any
other suitable rate.

The optical signal received by each light
sensor 2835 is monitored by a computer in real time.
15   Transformation of a material candidate or other
material on a region of the substrate from a solid to a
liquid state will generally cause an abrupt decrease in
the amount of light reaching the sensor that lies on
the optical path passing through that region or well.
20   This effect arises primarily because amorphous liquids
have a much weaker "birefringence polarizing effect" on
light than solid crystalline materials. The
temperature at which the optical signal associated with
a given region or well of the substrate changes can
25   then be detected by the computer and recorded, yielding
a measure of the melting point of that particular
sample. The entire array of materials on the substrate
or any subset thereof may be characterized for melting
points during a single thermal ramp-up cycle, as the
30   individual sensor corresponding to each region will
provide a distinct signal as the temperature of the

- 142 -

entire substrate reaches the melting point associated
with the material located at said region.

Slower rates of temperature increase tend to
yield more accurate melting point values by reducing
5   transient errors associated with finite heat transfer
delays between the thermal platform and the substrate.
The actual ramp-up rate chosen for a given measurement
set will generally reflect a compromise between
accuracy and overall time required to complete the set.
10   In the case of polymorphs, it is possible to
measure more than simple melting points with this test,
inter-polymorph transitions may also be observed.
Inter-polymorph transitions may include transitions
from one polymorph to another (e.g., solid to solid
15   transitions). In this case, a detectable shift in the
intensity of filtered light reaching a sensor (where
the change may be an increase or a decrease) would
indicate a transition from one solid form to another,
particularly if the same region of the substrate
20   undergoes a melting transformation at some later time
and higher temperature during the set of measurements.

FIG. 30 illustrates an in-situ monitoring
assembly 3000, which can be used to observe
crystallization of library members in accordance with
25   the principles of the present invention. As shown, in-
situ monitoring assembly 3000 is positioned below work
surface 2330 of FIG. 23, which provides support for
devices such as thermal control chambers 2500. In this
configuration, work surface 2330 has optical pathways
30   leading to the regions (or vessels) where materials are
being formed so that in-situ monitoring device 3000 can

- 143 -

perform measurements. As further shown, assembly 3000
is capable of moving horizontally with respect to work
surface 2330 for positioning under various thermal
control chambers 2500. Assembly 3000 is positioned

5   beneath one of thermal control chambers 2500 to perform
in-situ measurement. If desired, assembly 3000 can be
positioned above work surface 2330 or part of work
surface 2330. In-situ measurements may provide an
advance indication of library members that have formed

10 crystal structures. This information can be provided,
for example, as input for determining which library
members should be selected for testing when the
crystallization step is complete.

        Also shown in FIG. 30 is an enlarged cross-

15 sectional view taken from circle 3. The cross-
sectional view shows how in-situ monitoring can be
accomplished using light source 3010, diffuser 3012,
polarizer 3014, light beam splitter 3016, second
polarizer 3018, lens 3020, and detector 3022. When

20 assembly 3000 is it preferably positioned such that the
crystallization assembly (e.g., crystallization
assembly 2100) contained within thermal control chamber
2500 is within full view of lens 3020. This enables
assembly 3000 to scan two or more library members

25 simultaneously. If lens 3020 is a telescentric lens,
then light received by the lens is able to transmit the
light in parallel to detector 3022, thereby reducing
image distortion caused by conventional lenses. When
detector 3022 captures the light signal, it is able to

30 provide a relatively clear picture of the material
samples. Detector 3022 can be, for example, a camera,

- 144 -

a digital camera, a television camera, a charge-coupled
device.

     Assembly 3000 operates on substantially the
same principles as that previously described in
5 conjunction with the birefringence testing mechanism of
FIG. 28. Instead of a transmission scanning technique,
however, assembly 3000 uses a reflective optical
scanning technique that detects reflection of light off
a crystalline structure. The reflective technique
10 operates generally as follows. Light emitted from
light source 3010, as indicated by the dotted line,
passes through diffuser 3012 and first polarizer 3014.
Then the light signal reaches beam splitter 3016, which
redirects a portion of the light signal towards the
15 material samples, as indicated by the change in the
illustrative light path. Light reflected from the
material samples passes back through beam
splitter 3016. If any portion of the light signal has
been altered by any of the material samples, then it
20 may pass through second polarizer 3018 that is rotated
90° from the first polarizer. Light that passes
through second polarizer 3018 is received by lens 3020
and then captured by detector 3022.

     Detector 3022 may capture an image of the
25 entire array of material samples or it may capture a
portion. If it captures a portion of the array,
assembly 3000 may be moved accordingly so that a
complete picture or detection of the array can be
obtained.

30   Use of assemblies 1500, 1600 and 2100 allow
for a complete workflow in the formulation of crystals

- 145 -

of drug candidates. In one embodiment, the workflow
begins with the original drug candidate being dispensed
into vials 1516 of reaction assembly 1500, either while
vials 1516 are in a separate rack or in reactor base
5 1514 (e.g., with bottom plate 1510 and shock-absorbent
layer 1512 attached to reactor base 1514). The drug
candidate can be in a solid state or in solution or
suspension, but any solvent present with the original
form of the drug candidate is removed, for example, by
10 evaporation, wicking, or other methods known to those
of skill in the art. The desired recrystallization
solvent or solvent mixtures selected as discussed above
are then dispensed into each vial 1516 in the desired
amounts (typically with sufficient solvent to form
15 saturated solutions in the vials). Optionally,
different acids, bases, or salts are added (as
discussed above in the salt selection process). Also
optionally, mixing objects are placed in the vials (for
example, using device 1402 such as in FIG. 14).

20   Barrier sheet 1518 and septum 1520 are placed
over vials 1516 in reactor base 1514 (with bottom
plate 1510 already attached) and reactor cover 1522 is
secured to reactor base 1514 with sufficient strength
to form seals over vials 1516. Assembled reaction
25 assembly 1500 is then placed in a heater, shown in
FIG. 23 (or FIGS. 24 and 25) and optionally placed on a
commercially available shaker (available through VWR
and made by IKA, MTS, WORKS or Lab-line). For a
desired amount of time (such as 2 hours or more, 4
30 hours or more or 8 hours or more) and at a desired
temperature (such as at least 40°C, at least 60°C or at

- 146 -

least 80°C), assembly 1500 is heated and optionally stirred or shaken to allow for dissolution and/or reaction.

Afterwards, reaction assembly 1500 is placed
5 on a work surface and a needle or pipette is used to sample the hot liquids in vials 1516. This is accomplished by inserting a needle or cannula through holes 1523, septum 1520 and barrier sheet 1518 and aspirating an aliquot of liquid (such as less than 1000
10 μL or less than 100 μL). The aliquot can be taken by hand or automatically, such as with the equipment shown in FIG. 23A as described above.

The aliquot of liquid is maintained in the needle or pipette that is moved to filtration assembly
15 1600, which is in an assembled state. The needle is placed into the first position as shown in FIGS. 20A and 20B, and extended through hole 1625A, septum 1620 and barrier sheet 1618 such that it is in sealing communication with small o-ring 1744. The liquid is
20 dispensed through needle 2020 into opening 2020 and the liquid is filtered through the filter 1634 before entering vials 1616. Filtering can occur at a desired temperature by placing filtration assembly 1600 into a heater such as described above in FIG. 23.

25   After filtration, the filtrates (typically at a desired temperature) are aspirated by placing needle 2020 through hole 1625B, as shown in Fig. 20C. Needle 2020 extends through hole 1625B, septum 1620, barrier sheet 1618, filter subassembly 1630 and into
30 vials 1616 to aspirate an aliquot of the liquid filtrate (e.g., less than 1000 μL or less than 100 μL

.- 147 -

of the filtrate). This filtrate is used for solubility
at temperature testing, as described herein.

The needle is then moved to crystallization
assembly 2100. The needle is extended through

5   holes 2177 in reactor cover 2176 through septum 2174,
barrier layer 2172 and into the crystallization
receptacle formed by side walls 2169. Liquid filtrate
is then dispensed into the receptacle. Liquid filtrate
can be dispensed to a number of different

10 crystallization assemblies, such as multiple
crystallization assemblies, glass microtiter plates and
the like so that crystallization occurs under a number
of different conditions or methods. After dispensing
into all receptacles, the crystallization assembly is

15 subjected to crystallization conditions, such as by
lowering the temperature of the assembly (e.g., below
about 35°C or below about 25°C or below about 15°C or
below about 5°C) for a desired amount of time (e.g.,
two hours or more, four hours or more or eight hours or

20 more).

After the allotted time, reactor cover 2176,
septum 2174, and barrier sheet 2172 are removed. In an
alternative embodiment, the crystallization assembly
can be used without reactor cover 2176, septum 2174 and

25 barrier sheet 2172, with the filtrate being deposited
directly into the crystallization chambers; with this
embodiment allowing for other crystallization
methodologies, such as evaporation. With reactor
cover 2176 removed, the mother liquor or supernatant is

30 sampled for solubility testing, as described herein.
Thereafter, the remainder of the mother liquor or

- 148 -

supernatant is removed by pipetting and/or wicking or
other methods and crystallization assembly 2100 is
disassembled providing an array of crystals on
substrate 2164. This array can then be screened, as
5   described herein. See Example 6 for an illustration of
using the assemblies described herein in a
crystallization workflow.

Although the above-described invention has
been described for drug candidate compounds, this
10 invention may be practiced with any compound of
interest, particularly low molecular weight compounds.
Thus, the methods, apparatus and systems described
herein may be used for any compound for which salt
selection and/or polymorph characterization is desired.
15   The following examples provide illustrative
examples on how the present invention can be used to
perform the processes described above. These examples
are for the purpose of illustration only and are not to
be construed as limiting the scope of the invention in
20 any way.

EXAMPLE 1: Caffeine - Salt Selection

A solution of caffeine in dichloromethane (25
mg/mL) was dispensed into ninety-six wells of an eight
by twelve microtiter plate reactor having removable
25 vials (shown in FIG. 15) that may be 750 µl in size
such that each well contained about 10 mg of caffeine.
After removal of the solvent by evaporation, seven
different solutions of acids in either dichloromethane
or tetrahydrofuran (THF) (the salt reactants) were
30 dispensed, with a different acid solution being

- 149 -

dispensed into each of the twelve wells in different rows of the microtiter plate and with the first row having no acid added (only the solvent dichloromethane).

5   The following acid solutions were added to the twelve wells of each rows two through eight: row two, acetic acid in dicholomethane; row three, benzene sulfonic acid in dicholomethane; row four, hydrochloric acid in dichloromethane; row five, methyl sulfonic acid

10   in dicholomethane; row six, succinic acid in THF; row seven, tartaric acid in THF; and row eight, toluene sulfonic acid in dichloromethane. One equivalent of acid was added to each well and the total volume was 400 µl. The reactor was sealed and shaken at room

15   temperature for four hours. The cover was removed and the solvents evaporated. Twelve different recrystallization solvents were added to the wells, with a different recrystallization solvent being added to the eight wells of each twelve different columns, as

20   follows: column one, ethylacetate; column two, ethanol; column three, methylethylketone; column four, nitromethane; column five, heptane; column six, aectonitrile; column seven, 2-propanol; column eight, p-dioxane; column 9, 2-methoxyethyl ether; column ten,

25   1-propanol; column eleven, toluene; and column twelve, water.

          The reactor was sealed and heated to 60°C and heated at that temperature for four hours. The cover was removed and aliquots (e.g., 200 µl) of each well

30   were removed by pipette and dispensed to a glass microtiter plate (from Zinsser Analytics). Another

- 150 -

aliquot was removed and added to an array of vials and
diluted with acetonitrile for further dilution and
liquid chromatography analyses, as described above in
order to obtain a solubility measurement of the

5   compound at 60°C. The glass microtiter plate was
sealed and placed in a Torrey Pines incubator at 70°C.
The temperature was ramped over 8 hours to 10°C. After
sitting at 10°C for at least ten hours, aliquots of the
mother liquor were removed and diluted with

10 acetonitrile for LC analysis, as described above. The
concentration of the caffeine in the mother liquor is
considered to be the solubility, with the results shown
in Table 4, below:

Table 4

0.00	4.88	14.54	25.96	0.00	17.36	3.98	18.57	10.88	4.45	4.74	26.72
0.00	4.77	12.77	25.67	0.00	16.58	4.03	18.43	10.26	4.55	5.85	26.14
8.13	4.82	14.54	25.21	0.00	18.82	3.97	19.94	11.12	4.28	5.21	25.38
7.65	5.25	14.88	18.74	0.00	12.96	3.90	13.70	11.13	4.19	4.96	25.04
4.17	5.19	9.26	24.28	0.00	16.33	3.58	3.34	2.88	4.22	2.65	25.21
5.29	4.96	14.37	25.58	0.00	16.72	4.07	21.53	11.31	4.45	4.54	24.49
2.96	5.58	11.35	18.35	0.00	5.63	5.05	25.40	12.45	5.19	4.53	25.16
0.17	5.38	7.50	25.90	0.00	3.52	3.78	3.71	0.94	4.48	0.47	25.66

Note that the solubility measurements at 60°C
and 10°C can be compared to obtain the mass of the

25 crystals obtained, which was obtained in this case.
The glass plate was then placed between cross
polarizing filters and scanned for wet birefringence.
The remaining mother liquor was removed by pipette and
residual solvent was removed by wicking with filter

30 paper. Another image was taken between cross
polarizing filter, giving dry birefringence.

- 151 -

Birefringence images of the solids in wells were
obtained under a microscope equipped with crossed
polarized filters. Raman spectra were obtained on
individual crystals in each of the wells, in accord
5   with the procedures described above.

EXAMPLE 2: Naproxen - Salt Selection
          A set of experiments, similar to Example 1,
was carried out using naproxen to form salts by
reaction with bases. The experimental set up was the
10   same as in Example 1, using a solution of naproxen in
dichloromethane (25 mg/mL) dispensed into 96 wells such
that each well contained 10 mg of naproxen. After
removal of the solvent by evaporation, seven different
solutions of bases in either methanol or water (the
15   salt reactants) were dispensed, with a different basic
solution being dispensed the twelve wells of different
rows of the microtiter plate and with the first row
having no base added (only the solvent methanol).
          The following basic solutions were added to
20   the twelve wells of each row: row two, sodium hydroxide
in methanol; row three, potassium hydroxide in
methanol; row four, calcium carbonate in water; row
five, ammonium hydroxide in methanol; row six,
ethylenediamine in methanol; row seven, L-arginine in
25   methanol; and row eight, pyridine in methanol. One
equivalent of base was added to each well and the total
volume was 400 µl.
          The reactor was sealed and shaken at room
temperature for four hours. The cover was removed and
30   the solvents evaporated. Twelve different

- 152 -

recrystallization solvents were added to the wells,
with a different recrystallization solvent being added
to the each of the eight wells of each different
column, as follows: column one, isopropyl acetate;
5   column two, ethanol; column three, heptane; column
four, acetonitrile; column five, 1-octanol; column six,
anhydrous p-dioxane; column seven, toluene; column
eight, 2-butanone; column nine, water; column ten,
nitromethane; column eleven, 1,2-dichloroethane; and
10 column twelve, triethylamine. The reactor was sealed
and heated to 60°C for four hours. The cover was
removed and aliquots (e.g., 200 µl) were removed by
pipette and dispensed to a glass microtiter plate (from
Zinsser Analytics).
15   Another aliquot was removed and added to an
array of vials and diluted with acetonitrile for
further dilution and liquid chromatography analyses, as
described above in order to obtain a solubility
measurement of the compound at 60°C. The glass
20 microtiter plate was sealed and placed in a Torrey
Pines incubator at 70°C. The temperature was ramped
over eight hours to 10°C. After sitting at 10°C
overnight, aliquots of the mother liquor were removed
and diluted with acetonitrile for solubility at 10°C by
25 liquid chromatography analysis, as described above.
The solubility of each of the salts in 1-octanol and
water at both 10°C and 60°C were obtained using LC and
plotted and used to calculate the partition
coefficient, which is expressed as log P and shown
30 below in Table 5 (pH values were not obtained):

- 153 -

Table 5

log P Values	Temperature	Temperature
Cation	10° C	60° C
None	1.51	1.64
Sodium	-0.94	-0.77
Potassium	-0.28	-0.22
Calcium	0.68	0.78
Ammonium	-0.57	-0.50
Ethylenediamine	-1.05	-0.84
L-Arginine	-0.74	-0.85
Pyridine	0.82	1.45

The values of this experiment in Table 5 can
be compared to the Log P value published in the
Physicians Desk Reference for Naproxen of 1.6-1.8 at pH
of 7.4. This experiment demonstrates that clearly
different salt forms of Naproxen were created during
this example.

The glass plate was placed between crossed
polarizing filters and scanned for wet birefringence.
The remaining mother liquor was removed by pipette and
residual solvent was removed by wicking with filter
paper. Another image was taken between crossed
polarizing filters for dry birefringence.

EXAMPLE 3: Phenylbutazone - Polymorph Study

A solution of phenylbutazone in
dichloromethane (25 mg/mL) was dispensed into wells of
a microtiter plate having removable vials (shown in
Figure 3) that were 750 µl in size such that each well

- 154 -

contained 10 mg of phenylbutazone. After removal of
the solvent by evaporation, 16 recrystallization
solvents were dispensed into the wells in the ratios
shown below in Table 6, such that the total volume was

5   600 µl of solvent generating a library that included 84
unique solvent compositions. For mixtures of solvents,
pure solvents were dispensed prior to mixing and mixed
in the wells. The ratios shown in Table 6 are v/v
ratios, thus for example 80/20 means 80 parts of the

10 first listed solvent and 20 parts of the second listed
solvent (i.e., 480 µl/120 µl). The recrystallization
solvents were water (W), heptane (H), ethanol (E),
dichloroethane (D), acetonitrile (A), methylethylketone
(K), toluene (T), dimethylsulfoxide (S), 1-propanol

15 (IP), nitromethane (NM), α,α,α- trifluorotoluene (FT),
2-propanol (2P), p-dioxane (I), 1-octanol (10),
propylacetate (PA), and cyclohexane (CH):

Table 6

1 100	2 80/20	3 60/40	4 40/60	5 20/80	6 100	7 100	8 80/20	9 60/40	10 40/60	11 20/80	12 100
E	E/W	E/W	E/W	E/W	W	H	D/T	D/T	D/T	D/T	T
A	A/W	A/W	A/W	A/W	W	H	H/FT	H/FT	H/FT	H/FT	FT
1P	1P/W	1P/W	1P/W	1P/W	W	H	H/D	H/D	H/D	H/D	D
I	I/W	I/W	I/W	I/W	W	H	H/PA	H/PA	H/PA	H/PA	PA
K	K/E	K/E	K/E	K/E	E	D	D/A	D/A	D/A	D/A	A
NM	NM/E	NM/E	NM/E	NM/E	E	D	D/S	D/S	D/S	D/S	S
H	H/E	H/E	H/E	H/E	E	D	D/2P	D/2P	D/2P	D/2P	2P
10	10/E	10/E	10/E	10/E	E	D	D/CH	D/CH	D/CH	D/CH	CH

The reactor was sealed and heated to 60°C for

30 four hours. The cover was removed and aliquots (e.g.,
200 µl) were removed by pipette and dispensed into

- 155 -

individual regions of a glass microtiter plate (from
Zinsser Analytics), creating an array of ninety-six
liquids. The Zinsser plate was sealed in the
crystallizer and placed in a Torrey Pines incubator at
5   70°C. The temperature was decreased to 10°C over an
eight hour time period. After sitting at 10°C
overnight, aliquots of the mother liquor were removed
and diluted with acetonitrile to determine the
solubility of phenylbutazone in the various solvents at
10   10°C by LC analysis.

        The remainders of the solvents were removed
by pipette and any residual solvent was removed by
wicking with filter. The glass plate was then placed
between cross polarizing filters and scanned for dry
15   birefringence were obtained under a microscope at 5x
equipped with crossed polarized filters. Raman spectra
were obtained on individual crystals in each of the
wells in an automated manner, as described above.
Selected spectra that show the differences between
20   polymorphs are shown in FIG. 9. All of the Raman
spectra collected were correlated and grouped using the
software described herein. FIG. 11 shows the spectra
by well in array format 2008 as well as the user inputs
into the software of minimum grouping correlation
25   coefficient (with suggested parameters in parentheses)
2002 and whether to use a fixed reference (input of 1)
or to use the first well as the reference (input of 0)
2004. FIG. 11 also shows the ability of the user to
change the width and height of the spectra images 2006.
30   FIG. 12 shows the output of the software with the
spectra grouped by similarity into twelve families.

- 156 -

The entire recrystallization process was
repeated with a different glass plate in the
crystallizer, this time dispensing the hot solutions
for recrystallization directly into the crystallizer
5   subassembly (shown in FIG. 21, as described herein) in
the same well format. The crystallizer subassembly was
sealed and placed in a Torrey Pines incubator at 70°C.
The temperature was decreased to 10°C over an eight
hour time period. After sitting at 10°C overnight,
10   aliquots of the mother liquor were removed and diluted
with acetonitrile to determine the solubility of
phenylbutazone in the various solvents at 10°C by LC
analysis. The remainders of the solvents were removed
by pipette and any residual solvent was removed by
15   wicking with filter paper. Disassembly of the
crystallizer gave crystals in array format, with each
crystal in a separate region on a flat glass substrate.
The glass substrate was then mounted vertically on an
X-ray diffraction machine, as described above and data
20   was acquired on selected elements. Comparison of the
XRD two theta plots clearly shows the presence of three
polymorphs, shown in FIG. 10.

EXAMPLE 4: Cimetidine - Polymorph Study

A solution of cimetidine in dichloromethane
25   (25 mg/mL) was dispensed into wells of a microtiter
plate having removable vials that were 750 µl in size
such that each well contained 10 mg of phenylbutazone.
After removal of the solvent by evaporation, sixteen
recrystallization solvents were dispensed as described
30   above in Example 3 and in Table 6, above. The reactor

- 157 -

was sealed and heated to 60°C for four hours. The
cover was removed and aliquots (e.g., 200 µl) of
individual samples were removed by pipette and
dispensed to the crystallization assembly (shown in
5   FIG. 21, as described herein) in the same well format.
Another aliquot was removed and added to an array of
vials and diluted with acetonitrile for further
dilution to determine the solubility of cimetidine in
the various solvents at 70°C by LC analysis. The
10   crystallizer assembly was sealed and placed in a Torrey
Pines incubator at 70°C. The temperature was ramped
over 8 hours to 10°C. After sitting at 10°C overnight,
aliquots of the mother liquor were removed and diluted
with acetonitrile for LC analysis. The solvents were
15   removed by pipette and residual solvent was removed by
wicking with filter. Removing the cover and
disassembly of the crystallizer gave crystals on a flat
glass substrate.
        The glass plate was then placed between cross
20   polarizing filters and scanned to obtain dry
birefringence and birefringence images of selected
wells were obtained under a microscope equipped with
crossed polarized filter. Raman spectra were obtained
on individual crystals in each of the wells as
25   described in the previous example.

EXAMPLE 5: Sample Code for Polymorph Characterization
        Various programming languages can be
implemented to build software that can perform
categorization of crystalline structures in accordance
30   with the principles of the present invention.

- 158 -

Listing 1, below, illustrates a portion of Java® code
that can be used to implement the categorization
process described in conjunction with FIG. 8.

Listing 1

```
5       package com.symyx.webapp.projects.polymorphs;
        import com.symyx.webapp.xydata.filereader.*;
        import com.symyx.webapp.xydata.*;
        import java.util.*;
        import java.io.*;

10      public class SignalProcessorPolymorphs {
        private SignalProcessorResultPolymorphs result_;
                public SignalProcessorResultPolymorphs result( ) {
                return result_; }
                public void result(SignalProcessorResultPolymorphs
15      theResult) { result_=
        theResult; }

                private SignalProcessorParametersPolymorphs
                parameters_;
                public SignalProcessorParametersPolymorphs
20      parameters() { return parameters_; }
                public void
                parameters(SignalProcessorParametersPolymorphs params)
                {
                parameters_= params; }

25      public Signal ProcessorPolymorphs() {
                this.initialize();
        }

                private void initialize() {
                        this.result(new
30                      SignalProcessorResultPolymorphs());
                        this.parameters(new
                        SignalProcessorParametersPolymorphs());
                }

        public void sort(Vector items, Vector baskets) {
35              if (items == null) {
                        return;
                }

                int itemCount = 0;
                float cc;
40              int i =0;
                int j = 0;
                XyDataSet theSet = null;
                XyDataSet[] xySets = new XyDataSet[2];
                Vector stdItems = null;
45              Vector stdBaskets = null;
                Vector ccScores = new Vector();
                Float score = null;
```

- 159 -

```
        Float topScore = null;
        int scoreIndex = 0;
        int topScoreIndex = 0;
        Vector. theForm = null;
5       int formCount = 0;
        float minCC = this.parameters().minGroupCC();
        boolean useFixedReference =
        this.parameters().useFixedReference();

        // standardize items to be sorted
10      itemCount = items.size();
        stditems = this.standardize(items);

        //System.out.println("made stditems");

        // standardize the known forms
        if (baskets != null) { // input not empty
15      stdBaskets = this.standardize(baskets);
        }
        else {
        // no known forms yet,
        // so create new vector and put the first item in
20      // there
        stdBaskets = new Vector();
        stdBaskets.add(stditems.elementAt(0));
        }

        //System.out.println("made stdBaskets");

25      // make form baskets
        for (j=0; j<stdBaskets.size(); j++) {
            theForm = this.result().addNewForm();
            theForm.add(stdBaskets.elementAt(j));
        }

30      for (i=0; i<itemCount; i++) {
        // clean out the old data
        ccScores.clear();

        // get the next item to be classified
        theSet = (XyDataSet)stditems.elementAt(i);
35      xySets[0] = theSet;

        //System.out.println("sorting item: " + i + " " + theSet);
        //System.out.println("xySets[0]: " + xySets[0]);

        // get the forms
        formCount = this.result().formCount();
40      //System.out.println("formCount=" + formCount);
        for (j=0; j<formCount; j++) {
            xySets[1] = (XyDataSet)this.result().getFormData(j,
            useFixedReference);
            //System.out.println("xySets[1]: " + xySets[1]);

45          // align the data sets
            XyDataMath.alignX(xySets);
```

- 160 -

```
                //System.out.println("xySets[0]: " + xySets[0]);
                //System.out.println("xySets[1]: " + xySets[1]);

                // run correlation
                cc = XyDataMath.corrcoef(xySets[0], xySets[1]);
5               xySets[1].fitness(cc);
                //System.out.println("cc=" + cc);

                // add to the vector
                ccScores.add(j, new Float(cc));
        }

10      // find out which is the best
        topScoreIndex = 0;
        topScore = (Float)ccScores.elementAt(topScoreIndex);
        for (j=0; j<formCount; j++)
                score = (Float)ccScores.elementAt(j);

15                      if (topScore.floatValue() < score.floatValue()){
                                topScore = score;
                                topScoreIndex = j;
                        }
                        //System.out.println("topScoreIndex=" +
20                      topScoreIndex);
        }

        //System. out. println("top score: "
        //+ topScore.floatValue());

        // qualified for one of the classified forms
25      if (Math.abs(topScore.floatValue()-1.0f) <
        java.lang.Float.MIN VALUE) {
        continue; // the same data set
        }
        else if (topScore.floatValue() >= minCC) {
30              theForm = this.result().getForm(topScoreIndex);
                theForm.add(theSet);
                //System.out.println("old Form");
        }
        else { // found a new form
35              theForm = this.result().addNewForm();
                theForm.add(theSet);
                //System.out.println("newForm added");
        }

        }
40      }

        /**
         * standardize the data sets by removing the slope from the
                data sets,
         * and perform normalization on them
45       */
        private Vector standardize(Vector theSets) {
                if (theSets == null) {
                        return null;
```

- 161 -

```
        }
        Vector stdSets = new Vector();
        XyDataSet theSet = null;
        String fileName = null;

5       int count = theSets.size();
        for (int i=0; i<count; i++) {
            //System.out.println("i:" + i);
            theSet = (XyDataSet)theSets.elementAt(i);

            //System.out.println("theSet:" +
10          //theSet.header().getPath());

            fileName = theSet.header().getDataName();

            theSet = XyDataMath.removeSlope(theSet);
            theSet = XyDataMath.normalize(theSet);

            theSet.header().setDataName(fileName);

15          stdSets.add(theSet);
        }

        return stdSets;
        }


20      public Vector loadData() {
            String baseDir = "D:/raman_data/sorted_forms/";
            String listFileName = "Z_all_forms.txt";
            String fileName = null;
            String filePath = null;
25          Vector fv = new Vector();
            TextFileReader dataReader = new
            TextFileReaderPolymorphsRaman();

            filePath = baseDir + listFileName;
            FileReader fileReader = null;
30          LineNumberReader reader = null;

        try {
            fileReader = new FileReader(filePath);
            reader = new LineNumberReader(fileReader);
        }
35      catch (IOException e) {
            e.printStackTrace();
        }

        XyDataSet xyData = null;
        int i=0;

40      try {
        while ((fileName = reader.readLine()) != null) {
            try {
                if (fileName.indexOf("%") >= 0) {
                    continue;
```

- 162 -

```
                                }
                                i++;

                                filePath = baseDir + fileName;

                                System.out.println("loading... "
          5                     +.filePath);

                                xyData = new XyDataSet();
                                dataReader.readFile(filePath, xyData);
                                fv.add(xyData);
                                //System.out.println(xyData.header().getDa
         10                     //taName());

                        }catch (Exception e) {
                            e.printStackTrace();
                        }
                        }
         15         }
                catch (Exception e1) {
                    e1.printStackTrace();
                }




                finally {
         20         if (reader != null) {
                        try {
                            reader.close();
                            }catch (IOException e) {
         25             }
                }

                return fv;
                }

                public static void main(String[] args) {
         30         SignalProcessorPolymorphs spp =
                    new SignalProcessorPolymorphs();

                    if (args.length > 0) {
                        spp.parameters().minGroupCC(java.lang.Float.pars
                        eFloat(args[0]));
         35             spp.parameters().useFixedReference(true);
                    }

                Vector unknowns = spp.loadData();
                System.out.println(".........");
                System.out.println("sorting...");

         40     spp.sort(unknowns, null);
                spp.result().printForms();
                }
```

- 163 -

EXAMPLE 6: Crystallization Workflow

An exemplary crystallization workflow is shown in Fig. 31. In the workflow, the crystallization

5 solvents 3101 and precipitation solvents 3103 of interest are placed in solvent rack 3105 for use in the workflow. Array 3110 comprising the drug candidate of interest (a salt or a neutral compound) from the reaction station is placed in reactor assembly 3120.

10 The array can be an 8 x 12 array (e.g., a 96-well plate) or any other array known in the art (e.g., a 384-well plate). Crystallization solvents from the solvent rack are deposited into the wells of the array and the array is equilibrated to at least partially

15 dissolve the drug candidate in the solvent. In one embodiment, 800 µL of the crystallization solvents are added to each well, although any volume of solvent may be used in accordance with this invention.

After the drug candidates have been

20 equilibrated with the crystallization solvents to form solution, the solutions are filtered in filtration assembly 3130. In one non-limiting embodiment, 650 µL is taken from each well of the reactor assembly and filtered in the filtration assembly and a 600 µL

25 aliquot of each sample is removed after filtration. The aliquots may then be daughtered for crystallization analysis and other analyses into one or more different apparatus. In one embodiment, 50 µL of each sample is aliquoted into liquid chromatography (LC) vials 3140

30 for determination of solubility at a high temperature; 250 µL from each sample is aliquoted into crystallizer

- 164 -

assembly 3145 to investigate crystallization by
cooling; 200 µL from each sample is aliquoted into
evaporation plate 3150 to investigate crystallization
by evaporation; and 100 µL of each sample is aliquoted

5   into precipitation plate 3155 along with 400 µL of a
precipitation solvent to investigate crystallization by
precipitation.

After crystallization, supernatants from the
samples subjected to crystallization in the

10   crystallizer assembly and precipitation plate are
collected. The supernatant from the crystallization
assembly may be aliquoted into LC vials 3165 for
determination of the solubility of the drug candidate
at a cold temperature (e.g., room temperature or

15   below). The supernatant may be collected at station
3160 for any purpose desired, such as recycling or
discarding the drug candidate.

One having ordinary skill in the art
following the teachings of this invention would

20   recognize that one could use different combinations of
crystallization apparatus and/or methods. For
instance, one could provide a number of crystallizer
assemblies that use different crystallization
temperatures, or could use crystallizer assemblies to

25   perform precipitation or evaporation crystallization.
Further, one having ordinary skill in the art would
recognize that one could perform different non-
crystallization analyses using this workflow, such as
log P analyses.

30   All publications and patent applications
cited in this specification are herein incorporated by

.- 165 -

reference as if each individual publication or patent
application were specifically and individually
indicated to be incorporated by reference. Although the
foregoing invention has been described in some detail

5   by way of illustration and example for purposes of
clarity of understanding, it will be readily apparent
to those of ordinary skill in the art in light of the
teachings of this invention that certain changes and
modifications may be made thereto without departing

10 from the spirit or scope of the appended claims.

- 166 -

We claim:

1. A system for performing high throughput testing of a drug candidate to characterize polymorphs that form from said drug candidate, said system comprising:

a reactor assembly configured to contain a plurality of mixtures, said reactor assembly having a plurality of regions to contain said mixtures;

a crystallization assembly configured to contain said mixtures on a substrate, wherein said mixtures are subjected to crystallization conditions to provide at least one crystalline structure;

a temperature controlled housing configured to house a subassembly, said housing maintains said subassembly at a predetermined thermal profile;

at least two screening devices that obtain data on said at least one crystalline structure, wherein said at least two screening devices perform measurements on said at least one crystalline structure located on the same said substrate; and

a computer that controls said temperature controlled housing and receives data obtained by said screening devices, wherein said computer provides crystalline structure data obtained to a polymorph grouping algorithm, said polymorph grouping algorithm further configured to:

compare said data for said at least one crystalline structure with data of at least one polymorph family to obtain a best correlation coefficient; and

- 167 -

cluster said data associated with
said at least one crystalline structure into said at
least one polymorph family based on said best
correlation coefficient and selection criteria.

2.   The system according to claim 1 further
comprising a filter assembly that filters said mixtures
to provide substantially pure mixtures to said
crystallization assembly.

3.   The system according to claim 1 further
comprising a robotic pipette system that is controlled
by said computer.

4.   A system for performing a workflow, said
workflow including preparing and testing a plurality of
materials, said system comprising:
        a work surface;
        at least one assembly optionally mounted to
said work surface, wherein said at least one assembly
comprises:
                a reactor assembly;
                a filtration assembly; and/or
                a crystallization assembly;
        at least one thermal housing assembly mounted
to said work surface, said thermal housing assembly
configured to retain said at least one assembly; and
        a robotic material handling system mounted to
said work surface, said robotic material handling
system configured to (a) dispense said plurality of
materials into said at least one assembly and (b)

- 168 -

retrieve a plurality of mixtures formed from said
plurality of materials from said at least one assembly,
thereby preparing said plurality of materials for
testing.

5.   The system according to claim 4, wherein
said robotic handling system comprises a vented needle
assembly configured for maintaining a substantially
constant pressure within a sealed receptacle when
aspirating a liquid out of or dispensing liquid into
said sealed receptacle, said vented needle assembly
comprising:

a body having a main axis;

at least one guide rod that slides in
and out of said body along said main axis;

a guide block attached to said at least
one guide rod such that said guide block moves in
conjunction with said at least one guide rod;

a compressible spacer that provides
tension between said body and said guide block;

a venting needle coupled within said
guide block in parallel to said main axis, said venting
needle extending beyond a first side of said guide
block by a fixed length, thereby providing an open
passage through said guide block; and

a liquid handling needle coupled to said
body, in parallel to said main axis, said liquid
handling needle configured to pass through said guide
block.

6. A filtration assembly for filtering an array of solutions, comprising:

a reactor base having a plurality of receptacles;

a filtration subassembly having a plurality of first and second channels that are respectively associated with one of said plurality of receptacles, wherein at least one of the first plurality of channels includes at least one filter element, and wherein said plurality of second channels has no filter element and provides access to said associated receptacle; and

a filter cover that secures said filtration subassembly to said reactor base, said filter cover having a plurality of pairs of holes that align to said plurality of first and second channels.

7. The filtration assembly according to claim 6, wherein said filtration subassembly comprises:

a bottom layer that supports said at least one filter element, wherein said bottom layer has a pair of holes respectively associated with each one of said plurality of receptacles;

a sealing layer that secures said at least one filter element to said bottom layer, said sealing layer having pairs of holes that align with said pairs of the holes in said bottom layer, said sealing layer further configured to house a plurality of o-rings; and

a top layer that secures said plurality of o-rings to said sealing layer to form a

substantially airtight seal that isolates each pair of
said plurality of first and second channels from other
said pairs of first and second channels, said top layer
having pairs of holes that align with said pairs of
holes in said sealing layer such that said plurality of
first and second channels are provided.

8.   The filtration assembly according to
claim 6, further comprising a knife-edge ring
associated with each of said first plurality of first
channels, wherein each said knife-edge ring cuts each
of said at least one filter element to a fixed size.

9.   A crystallization assembly for
crystallizing at least one solution, comprising:
        a reactor having a first side and a
second side, said reactor having a plurality of
through-holes, each through-hole including a well
located on said second side;
        an o-ring that is configured to fit in
said well;
        a substrate that is secured to said
second side with a base cover, wherein said base cover
presses said substrate against said o-ring, thereby
providing an isolated region on said substrate that
corresponds to one of said plurality of through-holes;
and
        a reactor cover that secures a barrier
sheet to said first side such that said barrier sheet

seals said plurality of through-holes to isolate said at least one solution contained in one of said plurality of through-holes from said at least one solution contained in every other one of said plurality of through-holes, said reactor cover having a plurality of holes that each correspond to each one of said plurality of through-holes.

10. The crystallization assembly according to claim 9, wherein said plurality of o-rings are constructed in a two-dimensional array of said o-rings.

11. A reactor assembly for formulating an array of materials in a high-throughput mode, comprising:

a reactor base having a plurality of vials;

a barrier sheet mounted on a first side of said reactor base, said barrier sheet comprising a material that is pierceable;

a reactor cover that secures said barrier sheet to said reactor base such that said barrier sheet seals said plurality of vials to isolate said materials contained within each said plurality of vials, said reactor cover having a plurality of holes that each correspond to one of said plurality of vials; and

a reactor bottom that secures an elastic layer to a second side of said reactor base, wherein

- 172 -

said elastic layer provides tolerance for dimensional differences among said plurality of vials.

12. The reactor assembly according to claim 11, wherein said reactor cover further secures said plurality of vials within said reactor base.

13. A vented needle assembly configured for maintaining a substantially constant pressure within a sealed receptacle when aspirating a liquid out of or dispensing liquid into said sealed receptacle, comprising:

a body having a main axis;

at least one guide rod that slides in and out of said body along said main axis;

a guide block attached to said at least one guide rod such that said guide block moves in conjunction with said at least one guide rod;

a compressible spacer that provides tension between said body and said guide block;

a venting needle coupled within said guide block in parallel to said main axis, said venting needle extending beyond a first side of said guide block by a fixed length, thereby providing an open passage through said guide block; and

a liquid handling needle coupled to said body in parallel to said main axis, said liquid handling needle configured to pass through said guide block.

- 173 -

14. The assembly according to claim 13, wherein said compressible spacer is a spring.

15. A melting point detection assembly for measuring the melting points of an array of material samples supported on a substrate, said assembly comprising:

a thermal chamber that retains said substrate and controls a temperature of at least one region of said substrate;

a light system that provides at least one optical signal to said material samples and monitors said at least one optical signal to determine a melting point of said material samples; and

a computer system interconnected to said thermal chamber to control and monitor said at least one thermal profile, said computer system also being interconnected to said light system to obtain data provided by said at least one optical signal.

16. The assembly according to claim 15, wherein the light system is further configured to perform birefringence measurements on said material samples.

17. The assembly according to claim 15, wherein said light system is further configured to perform light scattering measurements on said material samples.

- 174 -

18.   A method for determining a melting point
for a plurality of crystalline structures, said method
comprising:

monitoring said plurality of crystalline
structures with an optical detection technique;

heating said plurality of crystalline
structures at a user-defined rate; and

recording a temperature for each one of
said plurality of crystalline structures when each one
of said plurality of crystalline structures undergoes a
phase transition.

19.   The method according to claim 18,
wherein said optical detection technique comprises a
transmissive birefringence testing technique.

20.   The method according to claim 18,
wherein said optical detection technique comprises a
reflective birefringence testing technique.

21.   The method according to claim 18,
wherein said optical detection technique comprises a
light scattering technique.

22.   An in-situ monitoring apparatus that
monitors a plurality of members that are subjected to
at least one crystallization condition, said apparatus
comprising:

a light projection system that transmits
at least one light signal to said plurality of members;

- 175 -

a light detection system that receives a
portion of said at least one light signal that is
reflected by said plurality of members, said light
detection system configured to monitor said plurality
of members for crystallization in-situ.

23.   The apparatus of claim 22, wherein said
light projection system comprises:
a light source that provides said at
least one light signal;
a beam splitter that redirects a portion
of said at least one light signal to one of said
plurality of members; and
a first polarization plate coupled
between said light projection system and said light
detection system, said first polarization plate
configured to block said at least one light signal that
is not altered by one of said plurality of members.

24.   The apparatus according to claim 22,
wherein said light detection system comprises:
a lens that receives each said at least
one light signal;
a detector that monitors each said
plurality of members in-situ to determine if a
crystalline structure forms in any of said plurality of
members.

25.   A method for monitoring, in-situ, a
plurality of members subjected to at least one
crystallization condition, said method comprising:

subjecting said plurality of members to
said at least one crystallization condition to promote
crystallization of said plurality of members;

monitoring said plurality of members in-
situ, wherein said monitoring is performed using a
reflective or transmissive birefringence optical
detection technique; and

obtaining data from said monitoring to
provide an indication if any of said plurality of
members have crystallized.

26. The method according to claim 25,
wherein said monitoring comprises:

providing at least one light signal to
said plurality of members;

reflecting said at least one light
signal from said plurality of members, wherein said at
least one light signal becomes at least one altered
light signal if said plurality of members contains at
least one crystalline structure; and

detecting said at least one altered
light signal.

27. The method according to claim 25,
wherein said determining comprises analyzing said data
to determine if any said plurality of members have
crystallized.

28. A method for selecting solvents for
polymorph generation and characterization or for salt
selection, comprising the steps of

providing a number of solvents to
produce a library of solvents;

providing one or more physical
properties or other characteristics for each the
solvents;

defining a selection criteria for one or
more of the physical properties or characteristics,
wherein the selection criteria permits the library to
be divided into at least two groups based upon the
defined physical properties or characteristics;

sorting each solvent of the library into
a group depending upon the selection criteria, wherein
each member of the group is similar to one another for
the defined physical properties or characteristics; and

selecting at least one solvent from each
group to perform polymorph generation and
characterization or salt selection.

29.   The method according to claim 28,
wherein said physical properties or characteristics are
selected from the group consisting of chemical class,
molecular weight, density, molar volume, melting point,
boiling point, enthalpy of evaporation, Hildebrand
solubility parameter, dipole moment, log solubility in
water, partition coefficient, pKa in water and
dimethylsulfoxide, dielectric constant, ionization
potential, viscosity, cost of solvent, cost of
disposal, degree of toxicity and degree of
environmental safety.

- 178 -

30.   The method according to claim 28,
further comprising the steps of:

providing an array wherein each well
contains a drug candidate and each row of the array
contains a different salt reactant, wherein the salt
reactant is selected from the group consisting of an
acid, a base, an amine or a salt solution;

reacting the drug candidate with the
salt reactant under conditions in which a drug
candidate salt will form;

selecting a number of different solvents
equal to the number of columns in the array;

adding the solvent to each column of the
array such that each column contains a different
solvent, wherein the columns of the array are
perpendicular to the rows of the array;

mixing the solvent with the drug
candidate salt under conditions in which drug candidate
crystals or precipitates may be formed; and

determining under what conditions a drug
candidate crystal or precipitate is formed.

31.   A method for performing high throughput
testing of a drug candidate or salt thereof to
characterize polymorphs that form from said drug
candidate or salt thereof, the method comprising:

preparing a library having a plurality of
members, each said member comprising said drug
candidate or salt thereof and at least one solvent;

subjecting said members to at least one
crystallization condition to produce at least one

- 179 -

crystalline structure of said drug candidate or salt
thereof, said at least one crystalline structure having
a crystal and a supernatant;

        screening said crystal of each of said at
least one crystalline structure to obtain data for each
of said crystals; and

        characterizing each said crystal based on
said data.

        32. The method according to claim 31,
wherein said characterizing comprises:

        comparing said data of each of said crystals
to data of said at least one polymorph family to obtain
at least one correlation coefficient; and

        categorizing said data of each of said
crystals to one of said at least one polymorph family
based on said at least one correlation coefficient and
selection criteria.

        33. The method according to claim 32,
further comprising the step, prior to said comparing
step, of assigning said data associated with one of
said crystals to a polymorph family.

        34. The method according to claim 31,
wherein said screening comprises screening said members
with at least two tests selected from the group
consisting of solubility, log P, melting point,
birefringence, hygroscopicity, infrared spectroscopy,
near infrared spectroscopy, Raman spectroscopy, X-ray
diffraction, UV-Vis spectroscopy, nuclear magnetic

- 180 -

resonance spectroscopy, gas chromatography, and liquid
chromatography testing.

35. A method for performing high throughput
salt selection for a drug candidate, the method
comprising:

preparing a library having a plurality of
members, each member comprising said drug candidate, a
salt reactant and at least one library solvent;

reacting said drug candidate and said salt
reactant under conditions to a produce drug candidate
salt;

adding said at least one library solvent to
said drug candidate salt to form said members;

subjecting said members to at least one
condition to produce at least one crystalline structure
of said drug candidate salt, said at least one
crystalline structure having a crystal and a
supernatant;

screening said crystal and said supernatant
to obtain data, wherein said data comprises at least
two selected from the group consisting of solubility,
log P, melting point, birefringence, infrared
spectroscopy, near infrared spectroscopy, Raman
spectroscopy, X-ray diffraction, hygroscopicity, UV-Vis
spectroscopy, nuclear magnetic resonance spectroscopy,
gas chromatography, and liquid chromatography testing;
and

selecting at least one said drug candidate
salt of interest.

- 181 -

36.   The method according to claim 35,
further comprising isolating said drug candidate salt
after said reacting.

37.   The method according to claim 35,
further comprising filtering said members after said
adding.

38.   A method for obtaining solubility data
from at least one crystallized structure of a drug
candidate or salt thereof, said method comprising:
              subjecting an array of materials to
crystallization conditions to form said at least one
crystalline structure, wherein said crystalline
structure comprises a crystal and a supernatant;
              extracting said supernatant from said at
least one crystalline structure such that said crystal
resides on a substrate;
              subjecting said supernatant to
solubility testing to obtain solubility data;
              screening said crystal to obtain crystal
data; and
              categorizing said at least one
crystalline structure into either a new polymorph
family or at least one polymorph family based on said
solubility data and said crystal data.

39.   The method according to claim 38,
wherein said solubility testing comprises using a
testing technique selected from the group consisting of
liquid chromatography, thin layer chromatography, gas

- 182 -

chromatography, infrared, fluorescence, log P and
ultra-violet absorption.

40. The method according to claim 38,
wherein said screening comprises screening said crystal
with a test selected from the group consisting of
melting point, birefringence, hygroscopicity, infrared
spectroscopy, near infrared spectroscopy, Raman
spectrosocopy, X-ray diffraction, UV-Vis spectroscopy,
nuclear magnetic resonance spectroscopy and gas
chromatography.

41. A method for testing and categorizing a
plurality of crystalline structures formed from a drug
candidate or salt thereof, said method comprising:
        preparing said plurality of crystalline
structures;
        screening said plurality of crystalline
structures with at least two different screening
techniques to obtain data on said crystalline
structures;
        comparing said data of each of said
crystalline structures to data of said at least one
polymorph family to obtain at least one correlation
coefficient; and
        categorizing said data of each of said
crystalline structures to one of said at least one
polymorph family based on said at least one correlation
coefficient and selection criteria.

- 183 -

42.   The method according to claim 41,
wherein said preparing comprises:
            preparing said plurality of library
members, each said library member comprising said drug
candidate or salt thereof; and
            subjecting said library members to at
least one condition to produce said plurality of
crystalline structures.

43.   A method for categorizing a plurality of
crystalline structures, said method comprising:
            providing at least one polymorph family;
            selecting one of said plurality of
crystalline structures;
            comparing said selected crystalline
structure to each said at least one polymorph family,
wherein each said comparison produces a correlation
coefficient;
            obtaining a best correlation coefficient
among each said correlation coefficient produced;
            categorizing said selected crystalline
structure to either (a) said at least one polymorph
family or to (b) a new polymorph family based on said
best correlation coefficient.

44.   The method according to claim 43,
wherein said providing comprises assigning one of said
plurality of crystalline structures to said at least
one polymorph family.

- 184 -

45. The method according to claim 43,
wherein said providing comprises obtaining said at
least one polymorph family from a database.

46. A method for performing high throughput
testing of a drug candidate or salt thereof to
characterize crystalline structures that form from said
drug candidate or salt thereof, the method comprising:
    preparing a plurality of members, each
said member comprising said drug candidate or salt
thereof and at least one solvent;
    subjecting said members to at least one
crystallization condition to produce at least one
crystalline structure of said drug candidate or salt
thereof, said at least one crystalline structure having
a crystal and a supernatant;
    screening said at least one crystalline
structures with at least two different screening
techniques to obtain at least crystallinity and
identity data on said crystalline structures; and
    characterizing said crystalline
structures.

47. The method according to claim 46,
wherein prior to said subjecting step, each of said
plurality of solutions is subjected to either (1)
filtering to remove possible solids or (2) daughtering
or (3) both filtering and daughtering.

48. A method for performing high throughput
testing of a drug candidate or salt thereof to

characterize crystalline structures that form from said
drug candidate or salt thereof, the method comprising:

preparing a plurality of members, each
said member comprising said drug candidate or salt
thereof and at least one solvent;

subjecting said members to at least one
crystallization condition to produce at least one
crystalline structure of said drug candidate or salt
thereof, said at least one crystalline structure having
a crystal and a supernatant;

screening said at least one crystalline
structure with at least two different screening
techniques to obtain at least crystallinity and
identity data on said crystalline structures; and

characterizing said plurality of
crystalline structures according to said crystallinity
and identity data.

49.   The method according to claim 48,
wherein prior to said subjecting step, each of said
plurality of solutions is subjected to either (1)
filtering to remove possible solids or (2) daughtering
or (3) both filtering and daughtering.

FIG. I

200   2/41

```
┌─────────────────────────────────┐
│ COMPUTER GENERATED              │──── 210
│ LIBRARY                         │
│    ┌──────────────────────┐     │
│    │     USER INPUT       │     │
│    └──────────────────────┘     │
└─────────────────────────────────┘
                │
                ▼                           ── 212
┌─────────────────────────────────┐
│ REACT DRUG CANDIDATES AND       │◄──────────────┐
│ SALT REACTANTS TO PRODUCE       │      ┌ ─ ─ ─ ─ ─ ─ ┐
│ DRUG CANDIDATE SALTS            │◄──── │ OPTIONAL    │
└─────────────────────────────────┘      │  MIXING     │
                │                         │ SOLVENT     │
                ▼                         └ ─ ─ ─ ─ ─ ─ ┘
┌ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ┐
│     ISOLATE DRUG              │── 214
│     CANDIDATE SALTS          │
└ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ┘
                │
                ▼                           ── 216
┌─────────────────────────────────┐
│ ADD LIBRARY SOLVENTS TO         │
│ DRUG CANDIDATE SALTS            │
└─────────────────────────────────┘
                │
                ▼                           ── 220
┌ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ┐
│   FILTER SYNTHESIZED         │
│     SOLUTION                 │
└ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ┘
                │
                ▼                           ── 222
┌─────────────────────────────────┐
│ CRYSTALLIZE DRUG                │
│ CANDIDATE SALTS                 │
└─────────────────────────────────┘
                │
                ▼                           ── 225
┌─────────────────────────────────┐
│ SCREEN EACH LIBRARY             │
│ MEMBER AND OBTAIN DATA          │
└─────────────────────────────────┘
                │
                ▼                           ── 230
┌─────────────────────────────────┐
│     ANALYZE THE DATA            │
└─────────────────────────────────┘
                │
                ▼                           ── 240
          ╱ DETERMINE ╲
         ╱ IF ANY SUITABLE DRUG ╲   NO
        ⟨  CANDIDATE SALTS ARE   ⟩──────────┐
         ╲   PRODUCED   ╱
          ╲     ?      ╱
                │ YES
                ▼
```

PROVIDE
LIBRARY
SOLVENTS

FIG.2A

TO STEP 250

200   **3/41**

```
          ┌─────────────────────┐
          │   FORMULATE BULK    │ ⟋ 250
          │ SAMPLES OF SUITABLE │
          │       SALTS         │
          └─────────────────────┘
                     │
                     ▼
          ┌─────────────────────┐
          │  SCREEN AND OBTAIN  │ ⟋ 255
          │  DATA FROM BULK     │
          │     SAMPLES         │
          └─────────────────────┘
                     │
                     ▼
          ┌─────────────────────┐
          │    ANALYZE BULK     │ ⟋ 260          TO STEP 212
          │    SAMPLE DATA      │                     ▲
          └─────────────────────┘                     │
                     │                                 │
                     ▼                                 │
              ╱─────────────╲  270                     │
             ╱  DETERMINE IF ╲                         │
            ╱   SALT IS       ╲      NO                │
            ╲  SUITABLE FOR   ╱ ──────────────────────┘
             ╲ DESIRED        ╱
              ╲ APPLICATION  ╱
               ╲     ?      ╱
                ╲─────────╱
                     │ YES
                     ▼
          ┌─────────────────────┐
          │   SUITABLE SALT     │ ⟋ 275
          │    DISCOVERED       │
          └─────────────────────┘
                     │
                     ▼
          ┌─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─┐
          │ IF DESIRED, PROCESS │
          │ MAY CONTINUE AT STEP│
          │   310 OF FIG. 3     │
          └ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ┘
```

FIG.2B

4/41

FIG.3

FIG. 4

<u>500</u>

```
┌──────────────────────┐
│  DEFINE SOURCES AND   │  510
│   LIBRARY LAYOUT      │
└──────────────────────┘
           │
           ▼
┌──────────────────────┐
│ DEFINE COMPOSITIONS   │  520
│      FOR EACH         │
│   LIBRARY MEMBER      │
└──────────────────────┘
           │
           ▼
┌──────────────────────┐
│  GENERATE RECIPE      │  530
│       FILE            │
└──────────────────────┘
```

FIG. 5

7/41

600

```
┌─────────────────────┐
│  DEFINE HARDWARE    │      610
│     RESOURCES       │
└─────────────────────┘
           │
           ▼
┌─────────────────────┐
│   ANALYZE LIBRARY   │
│ DESIGN TO DEVELOP   │      620
│ MATERIAL HANDLING   │
│    INSTRUCTIONS     │
└─────────────────────┘
           │
           ▼
┌─────────────────────┐
│  EXECUTE MATERIAL   │
│      HANDLING       │      630
│  INSTRUCTIONS TO    │
│ SYNTHESIZE LIBRARY  │
└─────────────────────┘
```

FIG. 6

FIG.7

FIG. 8

LIBRARY
MEMBER 1

LIBRARY
MEMBER 2

LIBRARY
MEMBER 3

LIBRARY
MEMBER 4

FIG.9

11 / 41

FIG.10

12/41

FIG.12

FIG.II

13/41

```
                                                                    1150
         1152                      1164
  ┌────────────────────────────────────────────────────────┐
  │ PARAMETERS                                         │ X │ │
  ├────────────────────────────────────────────────────────┤
  │                                                         │
1154 │  ┌─JUNK CLASSIFICATION──┐ ┌──MATCH ALGORITHM──┐     │ 1166
  │  │  ┌──┐ ┌──────┐          │ │ COVERAGE           │     │
  │  │  │✓ │ │ DO 1 │          │ │ ┌─────────────┬──┐ │     │ 1168
  │  │  └──┘ └──────┘          │ │ │ SINGLE      │ ▽│ │     │
1156 │  │                       │ │ └─────────────┴──┘ │     │
  │  │  MOVING AVERAGE POINTS  │ │ METHOD             │     │
  │  │  ┌──────────┐           │ │ ┌─────────────┬──┐ │     │ 1170
  │  │  │ 2        │           │ │ │ PEAK CENTER │ ▽│ │     │
1158 │  │  └──────────┘           │ │ └─────────────┴──┘ │     │
  │  │  MINIMUM PEAK HEIGHT    │ │ TYPICAL CC         │     │
  │  │  ┌──────────┐           │ │ ┌──────────┐       │     │ 1172
  │  │  │ 0.15     │           │ │ │ 0.8      │       │     │
1160 │  │  └──────────┘           │ │ └──────────┘       │     │
  │  │  MINIMUM ZERO CROSSINGS │ │ PEAK CENTER BAND WIDTH│  │
  │  │  ┌──────────┐           │ │ ┌──────────┐       │     │ 1174
1162 │  │  │ 2        │           │ │ │ 0.2      │       │     │
  │  │  └──────────┘           │ │ └──────────┘       │     │
  │  │  MAXIMUM ZERO CROSSINGS │ │ MIN PEAK HEIGHT    │     │
  │  │  ┌──────────┐           │ │ ┌──────────┐       │     │ 1176
  │  │  │ 50       │           │ │ │ 0.05     │       │     │
  │  │  └──────────┘           │ │ └──────────┘       │     │
  │  │                         │ │ MOVING AVERAGE POINTS │  │
  │  │                         │ │ ┌──────────┐       │     │
  │  │                         │ │ │ 3        │       │     │
  │  └─────────────────────────┘ └───────────────────┘     │
  │                                                         │
  │        ┌─────────┐  ┌──────┐  ┌────────┐               │
  │        │ DEFAULT │  │  OK  │  │ CANCEL │               │
  │        └─────────┘  └──────┘  └────────┘               │
  └────────────────────────────────────────────────────────┘
```

FIG. 11A

FIG.IIB   14/41

FIG.IIC

15/41

1272

PERFORM INITIAL SCREEN
AND OBTAIN DATA ON EACH
LIBRARY ELEMENT

1275

CRITERIA

1274

DOES A
PARTICULAR LIBRARY
ELEMENT MEET
CRITERIA
?

YES   NO

SELECT THE
PARTICULAR
LIBRARY ELEMENT
AS SUITABLE FOR
ADDITIONAL
TESTING

DISCARD THE
PARTICULAR
LIBRARY ELEMENT
AS ONE THAT IS
SUITABLE FOR
ADDITIONAL
TESTING

1276   1278

FIG. 12A

FIG.13

17/41

FIG.14A

FIG.14

18/41

1630

1610-1616

1625A,B

1617

1624

1620

1618

1600

FIG.16

1522

1521

1520

1518

1516

1515

1514

1512

1511

1523

1510

1500

1511

FIG.15

19/41

FIG.17

FIG.18

20/41

FIG. 19

FIG.20A

FIG.20B

22/41

FIG. 20C

FIG. 21

FIG. 21A

FIG. 21B

2104

FIG.21C

2168

2164

2106

2104

FIG. 22

2200

2206

2208

2208

2210

2210

2204

2212

2202

FIG. 22 A

2200

2206

2210

2202

2212

2204

FIG. 22B

FIG.23

FIG. 24

FIG.25

2570
2588
2587
2574
2589
2580
2572
2588
2588
2587
2586
2582
2500
2588
2100

FIG.26

FIG. 27

FIG. 27A

FIG.28

35/41

FIG.28A

FIG. 28B

FIG.29A

SOLVENT	CLASS	#	MW	n	Vm	MP	BP	ΔHvap	δ	μ	logS	logP	pKa	ε	IE	pKa+
TRIFLUOROACETIC ACID	ACID	1	114.02	1.48	77.0	-15	72	41	10.93	2.26	8.00	0.5	0.23	39	11.5	-8
FORMIC ACID	ACID	1	46.03	1.22	37.7	8	100	46.3	16.68	1.41	8.00	-0.540	3.75	51.1	11.33	-6
ACETIC ACID	ACID	1	60.05	1.04	57.7	15	115	51.6	14.26	1.74	8.00	-0.17	4.756	6.15	10.65	-6
PROPIONIC ACID	ACID	1	74.08	0.993	74.8	-20.7	141	55	12.97	1.75	8.00	0.33	4.88	3.3	10.44	-6
METHANOL	ALCHOHOL	2	32.04	0.791	40.5	-98	64.7	37.83	14.44	1.70	8.00	-0.77	15.5	32.63	10.84	-205
ETHANOL	ALCHOHOL	2	46.07	0.816	58.5	-114	78	42.46	13.01	1.69	8.00	-0.31	15.9	24.30	10.48	-2
TRIFLUOROETHANOL	ALCHOHOL	2	100.4	1.373	73.1	-43	78	43.97	11.65	1.9	8.00	0.41	12.4	26.5	11.49	-4
2-PROPANOL	ALCHOHOL	2	60.1	0.785	76.6	-89.5	82.4	45.48	11.59	1.66	8.00	0.05	18.0	18.3	10.17	-2
T-BUTANOL	ALCHOHOL	2	74.12	0.775	95.8	25	83	46.74	10.52	1.64	8.00	0.36	19.0	17.7	9.9	-2
1-PROPANOL	ALCHOHOL	2	60.10	0.804	74.8	-127	97	47.5	12.00	1.68	8.00	0.25	16.1	20.1	10.22	-2
2-BUTANOL	ALCHOHOL	2	74.12	0.808	91.7	-115	98	49.86	11.11	1.70	2.258	0.61	17.6	16.56	9.88	-2
1-BUTANOL	ALCHOHOL	2	74.12	0.810	91.5	-80	117.7	52.42	11.42	1.66	1.801	0.88	16.1	17.8	9.99	-2
2-METHOXYETHANOL	ALCHOHOL	2	76.09	0.965	78.8	-85	124	45.2	11.38	2.20	8.00	-0.77	14.8	17.2	10.13	-3
3-METHYL-1-BUTANOL	ALCHOHOL	2	88.15	0.809	109.0	-117	130	55.63	10.80	1.82	1.427	1.16	16.1	14.7	10	-2
2-ETHOXYTHETHANOL	ALCHOHOL	2	90.12	0.93	96.9	-90	135	48.23	10.62	2.08	8.00	-0.32	14.8	29.6	9.6	-2
1-PENTANOL	ALCHOHOL	2	88.15	0.811	108.7	-78	137	57.04	10.95	1.80	1.342	1.51	16.1	13.6	10.0	-2
1-OCTANOL	ALCHOHOL	2	130.23	0.827	157.5	-15	196	70.98	10.20	1.76	-0.268	2.97	16.1	10.3	10	-2
ETHYLENE GLYCOL	ALCHOHOL	2	62.07	1.113	55.8	-13	197	65.6	16.45	2.28	8.00	-1.360	15.1	37.3	10.55	-3
WATER	WATER	3	18.105	1.000	18.1	0	100	43.98	23.41	1.85	8.00	-1.38	15.74	80.37	12.621	-1.74
FORMAMIDE	AMIDE	4	45.04	1.134	39.7	2	210	60.15	18.63	3.70	8.00	-1.510	13.7	110	10.16	-0.48
N,N-DIMETHYLFOMAMIDE	ALKYLAMIDE	5	73.09	0.944	77.4	-61	153	47.45	11.78	3.82	8.00	-1.01	50.2	36.7	9.13	-0.3
N,N-DIMETHYLACETAMIDE	ALKYLAMIDE	5	87.12	0.937	93.0	-20	165	45.6	10.53	3.81	8.00	-0.770	25.8	37.78	9.2	-0.19
BUTYL AMINE	AMINE	6	73.14	0.740	98.8	-49	78	35.84	8.98	1.0	8.00	0.97	35	5.4	8.73	10.77
DIISOPROPYL AMINE	AMINE	6	101.19	0.722	140.2	-61	84	34.72	7.42	1.13	2.041	-1.49	37.3	4.0	7.59	11.13
TRIETHYL AMINE	AMINE	6	101.19	0.726	139.4	-115	88.8	34.96	7.46	0.66	1.867	1.45	51	2.42	7.53	11.01
PYRIDINE	AMINE	6	79.10	0.978	80.9	-42	115	40.21	10.56	2.19	8.00	0.65	38.3	12.3	9.26	5.21
ETHYLENE DIAMINE	AMINE	6	60.01	0.899	66.8	9	118	45.01	12.34	1.99	8.00	-2.04	35	14.2	8.6	9.92
MORPHOLINE	AMINE	6	87.12	0.999	87.2	-6	129	42.40	10.46	1.5	8.00	-0.86	35	7.33	8.88	8.33
NITROMETNANE	NITRO	7	61.04	1.127	54.2	-29	101	38.36	12.58	3.46	2.061	-0.35	10.2	39.4	11.08	-12
NITROETHANE	NITRO	7	75.07	1.045	71.8	-90	114	41.6	11.41	3.65	1.672	0.18	10.9	28.0	10.92	-12
2-NITROPROPANE	NITRO	7	89.09	0.992	89.8	-93	120	41.3	10.16	3.73	1.230	0.93	11.4	26.74	10.74	-12
1-NITROPROPANE	NITRO	7	89.09	0.998	89.3	-108	132	43.39	10.47	3.66	1.176	0.87	8.5	24.70	10.78	-12
NITROBENZENE	NITRO	8	123.11	1.196	102.9	5	210	55.10	11.16	4.22	0.320	1.85	20	34.82	9.94	-10.7
ACETONE	KETONE	9	58.08	0.791	73.4	-94	56	31.27	9.68	2.88	8.00	-0.24	20	20.7	9.703	-7.2
2-BUTANONE	KETONE	9	72.11	0.805	89.6	-87	80	34.92	9.30	2.50	2.348	0.29	20.3	18.5	9.52	-7
METHYLISOPROPYL KETONE	KETONE	9	86.13	0.805	107.0	-92	94	36.87	8.77	2.8	1.778	0.84	21.5	10.37	9.31	-7
3-PENTANONE	KETONE	9	86.13	0.813	106.9	-40	102	38.68	9.04	2.82	1.682	0.99	20.3	17.0	9.31	-7
2-PENTANONE	KETONE	9	86.13	0.802	107.4	-78	105	38.46	8.95	2.70	1.637	0.91	21	15.4	9.38	-7
METHYLISOBUTYL KETONE	KETONE	9	100.16	0.801	125.0	-80	117	40.65	8.54	2.7	1.279	1.31	21	13.11	9.3	-7
CYCLOPENTANONE	KETONE	9	84.12	0.951	88.5	-51	130	42.77	10.43	3.13	0.963	0.63	19.4	13.58	9.26	-7
CYCLOHEXANONE	KETONE	9	98.15	0.947	103.6	-47	155	45.09	9.91	3.24	0.398	0.81	20.1	18.2	9.16	-7
ETHYLFORMATE	ESTER	10	74.08	0.917	80.8	-80	53	32.11	9.36	1.93	1.945	0.230	53	7.2	10.61	-6.5
METHYL ACETATE	ESTER	10	74.08	0.932	79.5	-98	58	32.5	9.50	1.72	2.388	0.18	23.3	6.68	10.25	-6.5

SOLVENT	CLASS	#	MW	n	V_m	MP	BP	ΔH_{vap}	δ	μ	logS	logP	pKa	ε	IE	pK_{a+}
ETHYL ACETATE	ESTER	10	88.11	0.902	97.7	-84	77	35.69	9.01	1.78	1.903	0.73	24.5	6.02	10.01	-6.5
ISOPROPYL ACETATE	ESTER	10	102.13	0.872	117.1	-73	89	37.2	8.42	1.8	1.490	1.02	23.3	6.3	9.99	-6.5
PROPYL ACETATE	ESTER	10	102.13	0.888	115.0	-95	102	39.77	8.80	1.78	1.276	1.24	22.8	6.002	10.04	-6.5
ISOBUTYL ACETATE	ESTER	10	116.16	0.868	133.8	-99	118	35.9	7.73	1.86	0.799	1.760	24	5.07	9.97	-6.5
BUTYL ACETATE	ESTER	10	115.16	0.882	131.7	-78	125	43.89	8.67	1.87	0.924	1.78	22.4	5.01	9.92	-6.5
ACETONITRILE	NITRILE	11	41.05	0.786	52.2	-48	81	33.4	11.90	3.92	8.00	-0.34	25	37.5	12.2	-11
PROPIONITRILE	NITRILE	11	55.08	0.772	71.3	-93	97	38.19	10.63	4.02	8.00	0.16	25.2	29.7	11.85	-11
BUTYRONITRILE	NITRILE	11	69.11	0.794	87.0	-112	118	39.41	10.07	3.82	0.519	0.53	25	20.7	11.2	-11
BENZONITRILE	NITRILE	12	103.12	1.01	102.1	-13	191	55.48	11.14	4.18	0.301	1.56	37.5	26.0	9.73	-10
DIMETHYL SULFOXIDE	SULFOXIDE	13	78.13	1.101	71.0	18	189	52.89	13.03	3.96	8.00	-1.35	24.5	48.45	9.1	-0.65
DIETHYL ETHER	ETHER	14	74.12	0.715	103.7	-116	34.8	27.37	7.58	1.15	1.781	0.89	53	4.335	9.51	-2.39
METHYL-T-BUTYL ETHER	ETHER	14	88.15	0.740	119.1	-109	56	30.04	7.44	1.2	1.708	1.24	53	5	9.48	-3.5
DIMETHOXYMETHANE	ETHER	14	76.09	0.852	89.3	-105	64	28.89	8.41	0.74	8.00	0.22	53	2.7	9.7	-3.5
TETRAHYDROFURAN	ETHER	14	72.11	0.889	81.1	-108	66	32.16	9.35	1.63	8.00	0.46	53	7.58	9.4	-2.08
ISOPROPLY ETHER	ETHER	14	102.17	0.725	140.9	-85.5	68	32.26	7.11	1.13	0.944	1.488	53	3.88	9.20	-3.5
1.2-DIMETHOXYETHANE	ETHER	14	90.12	0.867	103.9	-58	85	38.47	8.84	2.08	8.00	-0.21	53	7.3	9.3	-3.5
PROPYL ETHER	ETHER	14	102.18	0.736	138.8	-123	89	35.79	7.57	1.21	0.690	2.03	53	3.3	9.3	-3.5
1.4-DIOXANE	ETHER	14	88.11	1.034	85.2	11.8	101	38.66	10.07	0.00	8.00	-0.27	53	2.209	9.19	-2.92
1.2-DIETHOXYETHANE	ETHER	14	118.18	0.842	140.4	-74	121	43.27	8.33	0.00	1.923	0.66	53	3.90	9.2	-3.5
BUTYL ETHER	ETHER	14	130.23	0.764	170.5	-98	142	45.0	7.72	1.17	-0.523	3.21	53	3.08	9.28	-3.5
BENZENE	AROMATIC	15	78.12	0.874	89.4	5.5	80	33.93	9.17	0.00	0.253	2.13	40	2.284	9.244	-16
TOLUENE	AROMATIC	15	92.14	0.885	106.5	-93	110.8	38.03	8.94	0.36	-0.279	2.73	37	2.379	8.828	-14
O-XYLENE	AROMATIC	15	106.17	0.860	123.5	-24	140	43.45	8.91	0.62	-0.750	3.12	38	2.568	8.56	-13
CUMENE	AROMATIC	15	120.19	0.864	139.1	-96	153	45.15	8.56	0.79	-1.246	3.66	38	2.38	8.73	-14
ANISOLE	AROMATIC	15	108.14	0.995	108.7	-37.5	154	46.91	9.68	1.38	0.017	2.11	46.0	4.33	8.2	-6.2
MESITYLENE	AROMATIC	15	120.19	0.884	139.1	-45	163	47.51	8.80	0.00	-1.317	3.42	40	3.4	8.4	-10
TETRALIN	AROMATIC	15	132.2	0.973	135.9	-35	207	55.23	9.63	0.60	-1.328	3.49	38	2.76	8.46	-13
PENTANES	HC	16	72.15	0.626	115.3	-130	36	26.75	7.09	0.00	-1.420	3.39	50	1.844	10.28	-20
HEXANES	HC	16	86.18	0.659	130.8	-95	69	31.73	7.31	0.00	-2.022	3.9	50	1.890	10.13	-20
CYCLOHEXANE	HC	16	84.16	0.779	108.0	6.5	80.7	33.12	8.23	0.00	-1.260	3.44	52	2.023	9.88	-20
HEPTANE	HC	16	100.20	0.684	146.5	-91	98	36.66	7.47	0.00	-2.469	4.397	50	1.925	9.93	-20
ISOOCATANE	HC	16	114.23	0.692	165.1	-107	98	35.24	6.89	0.1	-2.613	4.09	50	1.94	9.89	-20
METHYLCYCLOHEXANE	HC	16	98.19	0.77	127.5	-126	101	35.44	7.88	0.1	-1.854	3.61	50	2.02	9.64	-20
OCTANE	HC	16	114.23	0.703	162.5	-57	126	41.53	7.58	0.00	-3.180	5.18	50	1.95	9.8	-20
DECANE	HC	16	142.29	0.73	194.9	-30	174	51.9	7.78	0.00	-4.284	5.01	50	1.99	9.65	-20
DECALIN	HC	16	132.21	0.896	147.6	-125	190	48.4	8.72	0.00	-3.051	4.20	50	2.18	9.35	-20
HEXAFLUOROBENZENE	ARYL HALIDE	17	186.06	1.612	115.4	-4	80	35.82	8.31	0.00	-0.469	2.55	60	2.03	9.88	-22
FLUOROBENZENE	ARYL HALIDE	17	96.10	1.024	93.8	-42	85	34.68	9.06	1.60	0.188	2.27	39	5.42	9.2	-16
A.A.A-TRIFLUOROTOLUENE	ARYL HALIDE	17	146.11	1.199	121.9	-29	102	37.67	8.31	2.86	-0.854	3.01	34.1	9.2	9.685	-17
OCTAFLUOROTOLUENE	ARYL HALIDE	17	236.06	1.668	141.7	-66	104	41.8	8.12	0.2	-1.921	3.98	60	2.1	10.2	-23
CHLOROBENZENE	ARYL HALIDE	17	112.56	1.107	101.7	-45	132	41.0	9.52	1.69	-0.303	2.84	37.5	5.708	9.07	-16
BROMOBENZENE	ARYL HALIDE	17	157.01	1.491	105.3	-31	156	44.54	9.77	1.70	-0.351	2.99	34.3	5.4	9.00	-15
1.2-DICHLOROBENZENE	ARYL HALIDE	17	147.00	1.306	112.8	-17	180	50.21	10.07	2.50	-0.607	3.43	32	7.75	9.08	-17

SOLVENT	CLASS	#	MW	n	V_m	MP	BP	ΔH_{vap}	δ	μ	logS	logP	pKa	ε	IE	pK_{a+}
1.1-DICHLOROETHENE	CHC	18	94.93	1.213	78.3	-122	31	26.74	8.61	1.34	0.352	2.13	38	4.6	9.81	-22
DICHLOROMETHANE	CHC	18	84.93	1.325	64.1	-97	40	29	9.94	1.60	1.115	1.25	30	9.08	11.33	-22
CHLOROFORM	CHC	18	119.38	1.492	80.0	-63	61	31.4	9.29	1.01	0.900	1.97	18	4.806	11.37	-22
1.1.1-TRICHLOROETHANE	CHC	18	133.40	1.338	99.7	-35	75	32.62	8.50	1.78	0.173	2.48	41	7.252	11	-22
1.2-DICHLOROETHANE	CHC	18	98.96	1.256	78.8	-35	83	35.22	9.97	0.00	0.930	1.48	35	10.3	11.07	-22
TRICHLOROETHENE	CHC	18	131.39	1.463	89.8	-85	87	34.52	9.25	0.77	0.041	2.42	26	3.42	9.46	-22
1.1.2-TRICHLOROETHANE	CHC	18	133.40	1.435	93.0	-37	112	40.26	9.86	1.25	0.645	1.89	23	9.4	11.0	-22
1.1.2.2-TETRACHLOROETHANE	CHC	18	167.85	1.586	105.8	-43	147	45.72	9.88	0.00	0.471	2.39	20	8.5	11.1	-22
CARBON TETRACHLORIDE	PCC	19	153.82	1.594	96.5	-23	76	32.54	8.63	0.00	-0.101	2.83	60	2.238	11.47	-22
TETRACHLOROETHYLENE	PCC	19	165.82	1.623	102.2	-22	121	39.72	9.33	0.00	-0.699	3.4	60	2.5	9.326	-22
PERFLUOROHEXANE	PFC	20	338.05	1.669	202.5	-87	59	31.02	5.80	0.00	-5.000	6.02	60	1.75	13.0	-25
PERFLUOROHEPTANE	PFC	20	388.05	1.745	222.4	-78	83	36.34	6.03	0.00	-6.000	6.99	50	1.8	12.9	-25
PERFLUOROOCTANE	PFC	20	438.06	1.766	248.1	-25	103	41.16	6.11	0.00	-7	7.95	60	1.8	12.8	-25
PERFLUORODECALIN	PFC	20	462.08	1.908	242.2	-10	142	44.51	6.44	0.00	-7	7.80	60	1.9	12.4	-25

FIG. 29C

2500

2330

BOTTOM
OF 2500

3016

3018

3020

3022

3012

3014

3010

3000

3

FIG.30

41/41

CRYSTALLIZATION WORKFLOW

8x12 ARRAY FROM SYNTHESIS STATION — 3110

3120

REACTOR ASSEMBLY (EQUILIBRATE)

650uL

3130

FILTRATION ASSEMBLY

600uL

CRYSTALLIZER ASSEMBLY 250 uL — 3145

3150

LC VIALS HOT 50 uL — 3140

EVAPORATION PLATE 200 uL

PRECIPITATION PLATE 100 uL — 3155

LC VIALS COLD 50 uL — 3165

SUPERNATANT 800 uL — 3160

400uL

800uL

CRYSTALLIZATION SOLVENTS — 3101

SOLVENT RACK — 3105

PRECIPITATION SOLVENTS — 3103

FIG. 31

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/16962

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7)   :   G01N 33/48
US CL   :   702/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
   U.S. : 702/19,22,27; 435/6,69.1; 422/50,68.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,125,235 A (PADILLA et al.) 26 September 2000, see especially the abstract and claims 1-40.	1-3 and 31-49
Y	US 3,673,290 A (BRUBAKER et al.) 27 June 1972, see especially column 3, line 18, through column 7, line 51.	6-12
Y	US 5,430,194 A (BARNER et al.) 04 July 1995, see especially column 20, line 53, through column 41, line 6.	1-49
Y	US 6,245,508 B1 (HELLER et al.) 12 June 2001, see especially the abstract and column 5, line 9, through column 8, line 68.	4-17 and 28-49
Y	US 5,641,681 A (CARTER) 24 June 1997, see especially the abstract and Figures 6, 9, and 11.	1-49
Y	US 6,027,565 A (BUGG et al.) 22 February 2000, see especially the abstract and Figures 1-28.	1-49
Y	US 6,129,828 A (SHELDON, III, et al.) 10 October 2000, see especially the abstract and Figures 1-19.	1-49

☐ Further documents are listed in the continuation of Box C.   ☐ See patent family annex.

*	Special categories of cited documents:	
"A"	document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search	Date of mailing of the international search report
01 December 2002 (01.12.2002)	10 DEC 2002
Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Ardin Marschel
Facsimile No. (703)305-3230	Telephone No. 703-308-0196

Form PCT/ISA/210 (second sheet) (July 1998)

Continuation of B. FIELDS SEARCHED Item 3:
EWST, BIOSIS, MEDLINE, WPI, BIOTECH ABS., EMBASE, covering terms: polymorph, robot, algorithm, computer, crystal, melting point, O-ring, filter, and solubility

THIS PAGE BLANK (USPTO)